# Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes

Editorial, see p 710

**BACKGROUND:** Patients with heterozygous familial hypercholesterolemia (FH) and coronary heart disease have high mortality rates. However, in an era of high-dose statin prescription after acute coronary syndrome (ACS), the risk of recurrent coronary and cardiovascular events associated with FH might be mitigated. We compared coronary event rates between patients with and without FH after ACS.

**METHODS:** We studied 4534 patients with ACS enrolled in a multicenter, prospective cohort study in Switzerland between 2009 and 2013 who were individually screened for FH on the basis of clinical criteria according to 3 definitions: the American Heart Association definition, the Simon Broome definition, and the Dutch Lipid Clinic definition. We used Cox proportional models to assess the 1-year risk of first recurrent coronary events defined as coronary death or myocardial infarction and adjusted for age, sex, body mass index, smoking, hypertension, diabetes mellitus, existing cardiovascular disease, high-dose statin at discharge, attendance at cardiac rehabilitation, and the GRACE (Global Registry of Acute Coronary Events) risk score for severity of ACS.

**RESULTS:** At the 1-year follow-up, 153 patients (3.4%) had died, including 104 (2.3%) of fatal myocardial infarction. A further 113 patients (2.5%) experienced nonfatal myocardial infarction. The prevalence of FH was 2.5% with the American Heart Association definition, 5.5% with the Simon Broome definition, and 1.6% with the Dutch Lipid Clinic definition. Compared with patients without FH, the risk of coronary event recurrence after ACS was similar in patients with FH in unadjusted analyses, although patients with FH were >10 years younger. However, after multivariable adjustment including age, the risk was greater in patients with FH than without, with an adjusted hazard ratio of 2.46 (95% confidence interval, 1.07–5.65; $P$=0.034) for the American Heart Association definition, 2.73 (95% confidence interval, 1.46–5.11; $P$=0.002) for the Simon Broome definition, and 3.53 (95% confidence interval, 1.26–9.94; $P$=0.017) for the Dutch Lipid Clinic definition. Depending on which clinical definition of FH was used, between 94.5% and 99.1% of patients with FH were discharged on statins and between 74.0% and 82.3% on high-dose statins.

**CONCLUSIONS:** Patients with FH and ACS have a >2-fold adjusted risk of coronary event recurrence within the first year after discharge than patients without FH despite the widespread use of high-intensity statins.

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## Clinical Perspective

### What Is New?

- With the use of clinical criteria proposed by several expert groups, the prevalence of familial hypercholesterolemia (FH) reached 5% in a large cohort of patients hospitalized with acute coronary syndrome (ACS) in Switzerland, which may be 10 times greater than in the general population.
- Although nearly all patients with FH were discharged on statins, mostly high-dose statins, only a few achieved the recommended low-density lipoprotein cholesterol levels 1 year after ACS.
- Patients with FH had a 2-fold increased risk of coronary event recurrence within the first year after ACS compared with same-age patients without FH.

### What Are the Clinical Implications?

- These results demonstrate the necessity to measure low-density lipoprotein cholesterol and to encourage systematic screening for FH at the time of ACS.
- A better identification of patients with FH after ACS is required to individualize the intensity of lipid-lowering treatment and to better tailor secondary prevention because novel lipid-lowering drugs such as proprotein convertase subtilisin kexin 9 inhibitors are anticipated to further reduce the risk of coronary event recurrence in ACS patients with FH.

Heterozygous familial hypercholesterolemia (FH) is a common monogenic disorder associated with elevated low-density lipoprotein (LDL) cholesterol levels and premature coronary heart disease (CHD). Several definitions of FH have been proposed by expert groups that use LDL cholesterol and/or personal or family history of premature CHD.[1–3] Unfortunately, FH remains largely underdiagnosed in the general population, and many patients with FH are diagnosed only at the time of their first coronary event.[4] In Europe, up to 8% of adults hospitalized for acute coronary syndromes (ACS) have been shown to have clinical criteria compatible with FH,[5,6] which is >10 times greater than the prevalence of FH in the general population. However, even if FH is frequent among patients with premature CHD, there is still no established screening strategy to decrease the number of missed diagnoses.[7] Moreover, prognosis data are lacking in patients with FH in the setting of ACS, particularly in the era of widespread statin use.

The benefit of statins versus placebo on cardiovascular outcomes for patients with FH has never been established in a randomized, controlled trial.[8,9] Furthermore, very few data document the likelihood of cardiovascular event recurrence in patients with ACS with FH compared with those with no FH.[10] Thus, it is unknown whether further identification of FH is required for a more targeted secondary prevention approach, despite the widespread adoption of high-dose statins after ACS. Accordingly, we investigated whether a diagnosis of FH among ACS patients was associated with a greater recurrence risk of coronary events compared with ACS patients without FH independently of cardiovascular risk factors and severity of ACS.

## METHODS

### Study Population

The SPUM-ACS study (Special Program University Medicine-Acute Coronary Syndromes) is a prospective cohort study of consecutive patients hospitalized with ACS in Switzerland. The study was designed to identify new determinants and consequences of CHD. Details of the methods of the SPUM-ACS study have been reported previously.[11–13] Briefly, all patients hospitalized with ACS in 4 university hospitals in Switzerland were invited to participate with no exclusion criteria except severe physical disability, inability to give consent owing to dementia, and life expectancy of <1 year for noncardiac reasons. Inclusion criteria were age ≥18 years, a main diagnosis of ST-elevation–elevation myocardial infarction for patients presenting after pain onset, non–ST-segment–elevation myocardial infarction, or unstable angina. Overall, clinical follow-up information at 1 year was available for 5045 of patients included in the SPUM-ACS cohort study between September 2009 and September 2013. Baseline lipid measurements were missing for 453 patients (9%), and an additional 58 patients (1.3%) had missing family history information. Thus, the final population for this analysis included 4534 patients.

### Diagnosis of FH

The diagnosis of FH was based on 3 different definitions recommended by international guidelines (Tables I–III in the online-only Data Supplement). The latest statement of the American Heart Association combined LDL cholesterol >190 mg/dL and a family history of a first-degree relative with premature CHD.[1] The Simon Broome definition recommended by National Institute for Health and Care Excellence guidelines used total cholesterol >290 mg/dL or LDL cholesterol >190 mg/dL and a personal or family history of premature coronary disease.[3] Finally, the Dutch Lipid Clinic definition also used LDL cholesterol levels and a personal or family history of premature CHD. A possible FH was defined by a score of 3 to 5, and a probable/definite FH by a score of ≥6.[2] As done previously,[5] cutaneous signs and genetic tests of FH were counted as zero in all definitions because this type of information was missing for too many patients. For the Simon Broome definition in which such items are included, only a possible diagnosis of FH could be provided.

### Clinical Outcomes

The occurrence of clinical events during the first year after hospitalization for ACS was obtained by monitoring participants by telephone at 30 days after discharge and again in a clinical face-to-face visit at 1 year after ACS. Coronary events were defined as the occurrence of fatal or nonfatal myocardial infarction. Cardiovascular events were defined as the occurrence of myocardial infarction, ischemic stroke, transient ischemic

attack, or cerebrovascular or cardiovascular mortality. All cardiovascular end points used in this analysis were adjudicated by a panel of 3 certified cardiologists who served as independent experts blinded to the diagnosis of FH.

## Covariables

Total cholesterol, high-density lipoprotein cholesterol, and triglycerides levels were measured in the first blood draw at the emergency department within 24 hours of admission and immediately processed locally with standardized and certified dose methods. LDL cholesterol was calculated with the Friedewald formula when triglyceride levels were <394 mg/dL. LDL cholesterol was considered missing for patients with triglyceride levels of ≥394 mg/dL (1.9% missing). Lipid-lowering drugs that were taken before hospitalization and prescribed at discharge were systematically collected by trained study nurses. For patients using lipid-lowering drugs before hospitalization for ACS, we estimated untreated LDL cholesterol levels on the basis of the type and dose of lipid-lowering medication used before hospitalization, applying a correcting factor for LDL cholesterol adapted to the reported efficacy of each drug, as done previously for similar analyses.[6,14]

Pre-existing cardiovascular disease was defined as a previous diagnosis of CHD, ischemic cerebrovascular disease, or peripheral artery disease. Personal history of premature CHD was considered positive when men were <55 years old and women were <60 years old at the time of first ACS.[5] Family history of premature CHD was based on patient reports of a coronary event in a brother or father <55 years old or a mother or sister <60 years old. Education status was dichotomized as having graduated from high school or university or having a lower-level education. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs. Blood pressure–lowering drugs included all medications in the classes of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, diuretics, and nitrates. Smoking status was categorized into current, former, and never smokers. Former smokers were those who smoked at least 1 cigarette a day during at least 1 year and were nonsmokers for >1 month before inclusion. Diabetes mellitus was either self-reported or diagnosed by the use of antihyperglycemic medication or a hemoglobin $A_{1c}$ of ≥6.5% at admission.

## Statistical Analysis

At the time of hospitalization for ACS, we categorized patients according to the presence of FH for each definition and reported clinical characteristics in each group, as well as in patients not selected by any definition of FH. We assessed the associations between FH diagnosis and cardiovascular and coronary outcomes using unadjusted and multivariable Cox proportional hazard models. In the first model, we adjusted only for age and sex. In the second model, we adjusted for traditional cardiovascular risk factors, including age, sex, body mass index, current smoking, hypertension, and diabetes mellitus. In the third model, we further adjusted for high-intensity statins at discharge and attendance at cardiac rehabilitation. In the final model, we further adjusted for results of the 6-month prognosis GRACE (Global Registry of Acute Coronary Events) score to account for the severity of ACS. The GRACE risk score used to calculate long-term mortality or the composite of all-cause mortality or recurrent MI included age, heart rate, systolic blood pressure, initial serum creatinine, history of congestive heart failure, history of myocardial infarction, elevated cardiac markers (conventional troponins as per local laboratories), ST-segment depression, and in-hospital revascularization.[11,15] In an exploratory analysis, we further adjusted our final model to baseline LDL cholesterol levels to examine the role of LDL cholesterol in the risk of events among patients with FH. We applied a log transformation for LDL cholesterol because of right-skewed distribution.

For the coronary and cardiovascular events analysis, first events occurring within 1 year after the index hospitalization were considered (myocardial infarction, ischemic stroke, transient ischemic attack, cerebrovascular or cardiovascular mortality, all-cause death), and time to event was censored at 365 days after the index hospitalization.

To account for age differences between patients with FH and those without FH, we additionally assessed the prognosis of FH in young patients with premature CHD only and computed unadjusted Kaplan-Meier curves. Further sensitivity analyses were performed by including only patients who were not using lipid-lowering drugs at the time of hospitalization for ACS to account for the potential overestimation of FH prevalence with this method. All hypothesis tests were 2 sided, and the significance level was set at 5%. Statistical analyses were performed with STATA 14 (STATA Corp, College Station, TX).

## Ethics Statement

The Medical Ethics Committee of each center (Lausanne, Geneva, Bern, and Zurich) approved the study, and all participants gave written informed consent to participate in the study.

# RESULTS

Among 4534 patients hospitalized with ACS, 2.5% were identified with FH with the American Heart Association definition and 5.5% with the Simon Broome definition, whereas 18.2% were identified with possible FH and a further 1.6% with probable/definite FH with the Dutch Lipid Clinic definition. Overall, 79.2% of patients with ACS had no criteria for FH. Clinical characteristics of patients with and without FH are reported in Table 1. Compared with patients without FH, patients with FH were <10 years younger and presented more often with a first cardiovascular event and an ST-elevation–elevation myocardial infarction. Patients with FH identified with the American Heart Association definition were older, were more frequently women, and presented more frequently with hypertension than patients with FH identified with other definitions.

During the year after hospitalization for ACS, 153 patients (3.4%) died, 217 (4.8%) had a fatal or nonfatal myocardial infarction, and 275 (6.1%) experienced a cardiovascular event. Unadjusted rates of coronary and cardiovascular events were similar between patients with and without FH, but patients with FH were 10 years

**Table 1. Characteristics of Patients With ACS With and Without FH by Definition (n=4534)**

| | No FH | AHA FH | Simon Broome Possible FH | Dutch Lipid Clinic Possible FH (3–5 Points) | Dutch Lipid Clinic Probable/ Definite FH (>5 Points) |
|---|---|---|---|---|---|
| n | 3589 | 114 | 250 | 825 | 73 |
| Percentage | 79.2 | 2.5 | 5.5 | 18.2 | 1.6 |
| Demographics | | | | | |
| Age, y | 66.0 (11.3) | 55.6 (11.6) | 51.6 (9.8) | 52.3 (10.1) | 49.8 (9.3) |
| Female, n (%) | 746 (20.8) | 32 (28.1) | 55 (22.0) | 161 (19.5) | 16 (21.9) |
| White, n (%) | 3389 (94.4) | 107 (93.9) | 230 (92.0) | 766 (92.8) | 68 (93.1) |
| Higher education, n (%)* | 869 (27.9) | 29 (28.4) | 67 (29.5) | 228 (30.4) | 21 (30.9) |
| Smoking status, n (%) | | | | | |
| Never | 1168 (32.8) | 35 (30.7) | 66 (26.4) | 199 (24.3) | 19 (26.0) |
| Former | 1121 (31.6) | 29 (25.4) | 49 (19.6) | 149 (18.2) | 16 (21.9) |
| Current | 1263 (35.6) | 50 (43.9) | 135 (54.0) | 472 (57.6) | 38 (52.1) |
| Elevated alcohol use† | 450 (14.1) | 12 (11.5) | 24 (10.5) | 94 (12.4) | 9 (13.2) |
| Comorbidities | | | | | |
| Hypertension‡ | 2173 (60.6) | 52 (45.6) | 101 (40.4) | 318 (38.5) | 28 (38.4) |
| Diabetes mellitus§ | 711 (19.8) | 9 (7.9) | 28 (11.2) | 81 (9.8) | 4 (5.5) |
| Pre-existing CVD‖ | 955 (26.6) | 17 (14.9) | 33 (13.2) | 133 (16.1) | 8 (11.0) |
| Premature CHD¶ | 611 (17.0) | 62 (54.4) | 197 (78.8) | 660 (80.0) | 65 (89.0) |
| Family history# | 643 (17.9) | 114 (100) | 118 (47.2) | 452 (54.8) | 57 (78.1) |
| Objective measures | | | | | |
| Total cholesterol, mg/dL | 181.7 (42.5) | 270.7 (50.3) | 274.6 (50.3) | 224.3 (42.5) | 290.0 (61.9) |
| LDL cholesterol, mg/dL | 123.7 (34.8) | 224.3 (50.3) | 224.3 (42.5) | 166.3 (42.5) | 255.2 (65.7) |
| HDL cholesterol, mg/dL | 46.4 (15.5) | 46.4 (11.6) | 42.5 (11.6) | 42.5 (11.6) | 42.5 (11.6) |
| Triglycerides, mg/dL | 122.5 (96.2) | 122.5 (52.5) | 148.7 (113.7) | 131.2 (105.0) | 113.7 (43.7) |
| Body mass index, kg/m$^2$ | 27.0 (4.3) | 27.5 (4.8) | 27.6 (4.5) | 27.4 (4.4) | 28.2 (5.1) |
| eGFR, mL/min | 86.9 (27.2) | 90.9 (19.9) | 94.4 (23.4) | 98.8 (24.6) | 92.8 (19.6) |
| Medication at admission, n (%) | | | | | |
| Aspirin | 1132 (31.6) | 34 (29.8) | 60 (24.0) | 157 (19.0) | 25 (34.2) |
| Lipid-lowering drugs** | 1064 (29.6) | 43 (37.7) | 83 (33.2) | 188 (22.8) | 31 (42.5) |
| Statins | 1036 (28.9) | 40 (35.1) | 79 (31.6) | 184 (22.3) | 28 (38.4) |
| Antihypertensives†† | 1810 (50.4) | 37 (32.5) | 70 (28.0) | 228 (27.6) | 22 (30.1) |
| Type of ACS (n=4516), n (%) | | | | | |
| STEMI | 1886 (52.8) | 65 (57.0) | 148 (59.2) | 462 (56.2) | 46 (63.0) |
| NSTEMI | 1528 (42.7) | 45 (39.5) | 95 (38.0) | 325 (39.5) | 24 (32.9) |
| Unstable angina | 160 (4.5) | 4 (3.5) | 7 (2.8) | 35 (4.3) | 3 (4.1) |
| Severity of ACS | | | | | |
| Killip class III or above, n (%) | 156 (4.3) | 2 (1.7) | 4 (1.6) | 25 (3.0) | 0 (0) |
| Cardiac arrest, n (%) | 140 (3.9) | 3 (2.6) | 8 (3.2) | 3 (0.4) | 0 (0) |
| GRACE score for 6-mo mortality, points (n=4279)‡‡ | 139 (25) | 121 (22) | 114 (21) | 116 (22) | 114 (20) |

(*Continued*)

**Table 1. Continued**

| | No FH | AHA FH | Simon Broome Possible FH | Dutch Lipid Clinic Possible FH (3–5 Points) | Dutch Lipid Clinic Probable/ Definite FH (>5 Points) |
|---|---|---|---|---|---|
| Severity of coronary lesions, n (%) | | | | | |
| ≥2 Treated coronary lesions (n=4227) | 1198 (36.0) | 30 (27.3) | 64 (26.7) | 225 (28.7) | 17 (25.0) |
| ACC/AHA classification grade B2 or C any lesion (n=3497) | 1100 (39.7) | 29 (31.9) | 69 (33.7) | 216 (34.0) | 21 (38.2) |
| TIMI grade flow 0–II before PCI (n=3474)§§ | 1843 (67.6) | 64 (71.1) | 139 (66.8) | 461 (70.3) | 43 (72.9) |
| TIMI grade flow 0–II after PCI (n=3480)§§ | 118 (4.3) | 2 (2.2) | 7 (3.4) | 23 (3.5) | 1 (1.7) |

Data are given as mean (SD) when appropriate. ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; GRACE, Global Registry of Acute Coronary Events; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*Defined as a high school or university graduation or higher.

†Defined as >14 units of alcohol a week.

‡Defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs.

§Based on patient self-report, use of antihyperglycemic medication/insulin, or hemoglobin $A_{1c}$ ≥6.5%.

‖Defined as coronary heart disease, ischemic cerebrovascular disease, or peripheral artery disease.

¶Age of onset for ACS <55 years in men and <60 years in women.

#Self-reported history of a major cardiovascular event in a brother or father <55 years old or a mother or sister <60 years old.

**Include statins, fibrates, ezetimibe, niacin, and resins.

††Include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, or diuretics.

‡‡Include age, heart rate, systolic blood pressure, initial serum creatinine, history of congestive heart failure, history of myocardial infarction, elevated cardiac markers (conventional troponins as per local laboratories), ST-segment depression, and in-hospital revascularization.

§§Lowest TIMI flow per patient.

younger (Table 2 and Figure 1). In a multivariable model adjusted for age, sex, body mass index, current smoking, hypertension, diabetes mellitus, pre-existing cardiovascular disease, attendance at cardiac rehabilitation, prescription of high-intensity statins at discharge, and results of the 6-months GRACE risk score, patients with FH had a 2.46 increased risk of a recurrent coronary event compared with patients without FH (hazard ratio, 2.46; 95% confidence interval, 1.07–5.65; *P*=0.034) with the American Heart Association definition. The multivariable hazard ratio was 2.73 (95% confidence interval, 1.46–5.11; *P*=0.002) with the Simon Broome definition, and 3.53 (95% confidence interval, 1.26–9.94; *P*=0.017) with the probable/definite Dutch Lipid Clinic definition. For cardiovascular events, point estimates of the multivariable hazard ratio were slightly lower and reached statistical significance only with the Simon Broome definition (hazard ratio, 2.49; 95% confidence interval, 1.43–4.34; *P*=0.046). Further adjustment of the multivariable model with baseline LDL cholesterol levels did not decrease the point estimates of hazard ratios for coronary or cardiovascular events.

Comparisons of lipid management after ACS are reported in Table 3 for patients with and without FH. Among patients identified with FH according to at least 1 definition, 98.6% were discharged with any statins, and 77.3% were discharged with high-dose statins. One year after ACS, high-dose statins were still used by >70% of patients with FH, but <10% scored the 70-mg/dL LDL cholesterol target. Among patients without FH, 67% were discharged with high-dose statins, and 56% were still on high-dose statins 1 year after ACS, with nearly 38% reaching the 70-mg/dL LDL cholesterol target.

Stratified analyses performed in 1369 patients with premature CHD showed an increased risk of coronary events for patients with FH compared with patients without FH in both the unadjusted and multivariable-adjusted models (Table 4 and Figure 2). For cardiovascular events, statistical significance was reached for the Simon Broome definition only. Restricting the analysis to 3234 patients not using lipid-lowering drugs at baseline yielded roughly similar risk estimates but with larger confidence intervals (Table IV in the online-only Data Supplement).

## DISCUSSION

In this multicenter, observational study, the prevalence of FH was 1.6% to 5.5% (depending on which clinical definition of FH was used) among patients hospitalized

**Table 2. Risks of Recurrent Events After ACS With Respect to the Presence of FH (n=4534)**

| | AHA Definition | | Simon Broome Definition | | Dutch Lipid Clinic Definition | | |
|---|---|---|---|---|---|---|---|
| | No FH | FH | No FH | Possible FH | No FH (Score <3) | Possible FH (Score 3–5) | Probable/ Definite FH (Score >5) |
| Coronary events | | | | | | | |
| Events/participants, n | 211/4420 | 6/114 | 205/4284 | 12/250 | 185/3636 | 28/825 | 4/73 |
| Incidence rate, per 100 person-y | 5.0 | 5.6 | 5.0 | 5.0 | 5.4 | 3.5 | 5.7 |
| Unadjusted HR (95% CI) | 1.00 (Referent) | 1.10 (0.49;2.48) | 1.00 (Referent) | 0.99 (0.55–1.78) | 1.00 (Referent) | 0.66 (0.44–0.98) | 1.07 (0.40–2.87) |
| Age/sex–adjusted HR (95% CI) | 1.00 (Referent) | 1.65 (0.73–3.76) | 1.00 (Referent) | 1.95 (1.06–3.58) | 1.00 (Referent) | 1.32 (0.86–2.03) | 2.55 (0.92–7.03) |
| Model 1 adjusted HR (95% CI; n=4465)* | 1.00 (Referent) | 1.99 (0.87–4.53) | 1.00 (Referent) | 2.27 (1.23–4.18) | 1.00 (Referent) | 1.51 (0.97–2.35) | 3.14 (1.13–8.71) |
| Model 2 adjusted HR (95% CI; n=4423)† | 1.00 (Referent) | 2.33 (1.02–5.34) | 1.00 (Referent) | 2.51 (1.35–4.68) | 1.00 (Referent) | 1.60 (1.00–2.56) | 3.44 (1.23–9.63) |
| Model 3 adjusted HR (95% CI; n=4175)‡ | 1.00 (Referent) | 2.46 (1.07–5.65) | 1.00 (Referent) | 2.73 (1.46–5.11) | 1.00 (Referent) | 1.54 (0.94–2.52) | 3.53 (1.26–9.94) |
| Model 3 additionally adjusted for LDL cholesterol, HR (95% CI; n=4094) | 1.00 (Referent) | 2.92 (1.23–6.99) | 1.00 (Referent) | 3.73 (1.89–7.38) | 1.00 (Referent) | 1.92 (1.13–3.25) | 5.13 (1.71–15.43) |
| Cardiovascular events | | | | | | | |
| Events/participants, n | 267/4420 | 8/114 | 259/4284 | 16/250 | 236/3636 | 35/825 | 4/73 |
| Incidence rate, per 100 person-y | 6.4 | 7.5 | 6.4 | 6.7 | 6.9 | 4.4 | 5.7 |
| Unadjusted HR (95% CI) | 1.00 (Referent) | 1.17 (0.58–2.36) | 1.00 (Referent) | 1.05 (0.63–1.74) | 1.00 (Referent) | 0.64 (0.45–0.92) | 0.83 (0.31–2.23) |
| Age/sex–adjusted HR (95% CI) | 1.00 (Referent) | 1.72 (0.84–3.50) | 1.00 (Referent) | 2.02 (1.19–3.42) | 1.00 (Referent) | 1.25 (0.85–1.84) | 1.88 (0.67–5.16) |
| Model 1 adjusted HR (95% CI; n=4465)* | 1.00 (Referent) | 2.06 (1.01–4.21) | 1.00 (Referent) | 2.34 (1.37–3.97) | 1.00 (Referent) | 1.44 (0.97–2.13) | 2.31 (0.84–6.34) |
| Model 2 adjusted HR (95% CI; n=4423)† | 1.00 (Referent) | 1.98 (0.92–4.25) | 1.00 (Referent) | 2.31 (1.33–4.01) | 1.00 (Referent) | 1.47 (0.97–2.22) | 2.46 (0.89–6.80) |
| Model 3 adjusted HR (95% CI; n=4175)‡ | 1.00 (Referent) | 2.08 (0.97–4.48) | 1.00 (Referent) | 2.49 (1.43–4.34) | 1.00 (Referent) | 1.44 (0.94–2.21) | 2.49 (0.90–6.91) |
| Model 3 additionally adjusted for LDL cholesterol, HR (95% CI; n=4094) | 1.00 (Referent) | 2.39 (1.08–5.31) | 1.00 (Referent) | 3.27 (1.79–5.97) | 1.00 (Referent) | 1.71 (1.08–2.70) | 3.32 (1.14–9.69) |

ACS indicates acute coronary syndrome; AHA, American Heart Association; CI, confidence interval; FH, familial hypercholesterolemia; HR, hazard ratio; and LDL, low-density lipoprotein.

*Adjusted for age, sex, and cardiovascular risk factors, including body mass index, current smoking, hypertension, diabetes mellitus, and pre-existing cardiovascular disease.

†Model 1 additionally adjusted for prescription of high-intensity statins and attendance at cardiac rehabilitation at discharge.

‡Model 2 additionally adjusted for results of the 6-month GRACE (Global Registry of Acute Coronary Events) risk score.

for ACS, which demonstrates that the prevalence of FH may be 3 to 10 times greater than in the general population.[16,17] We further reported that patients with FH identified with clinical criteria had a >2-fold increase in risk of recurrent coronary events within 1 year after discharge compared with patients without FH after multivariable adjustment and despite more frequent use of high-intensity statins. This association between FH clinical diagnosis and recurrent coronary events was independent of cardiovascular risk factors and severity of ACS.

Previous studies assessed the cardiovascular risk of patients with FH compared with population-based

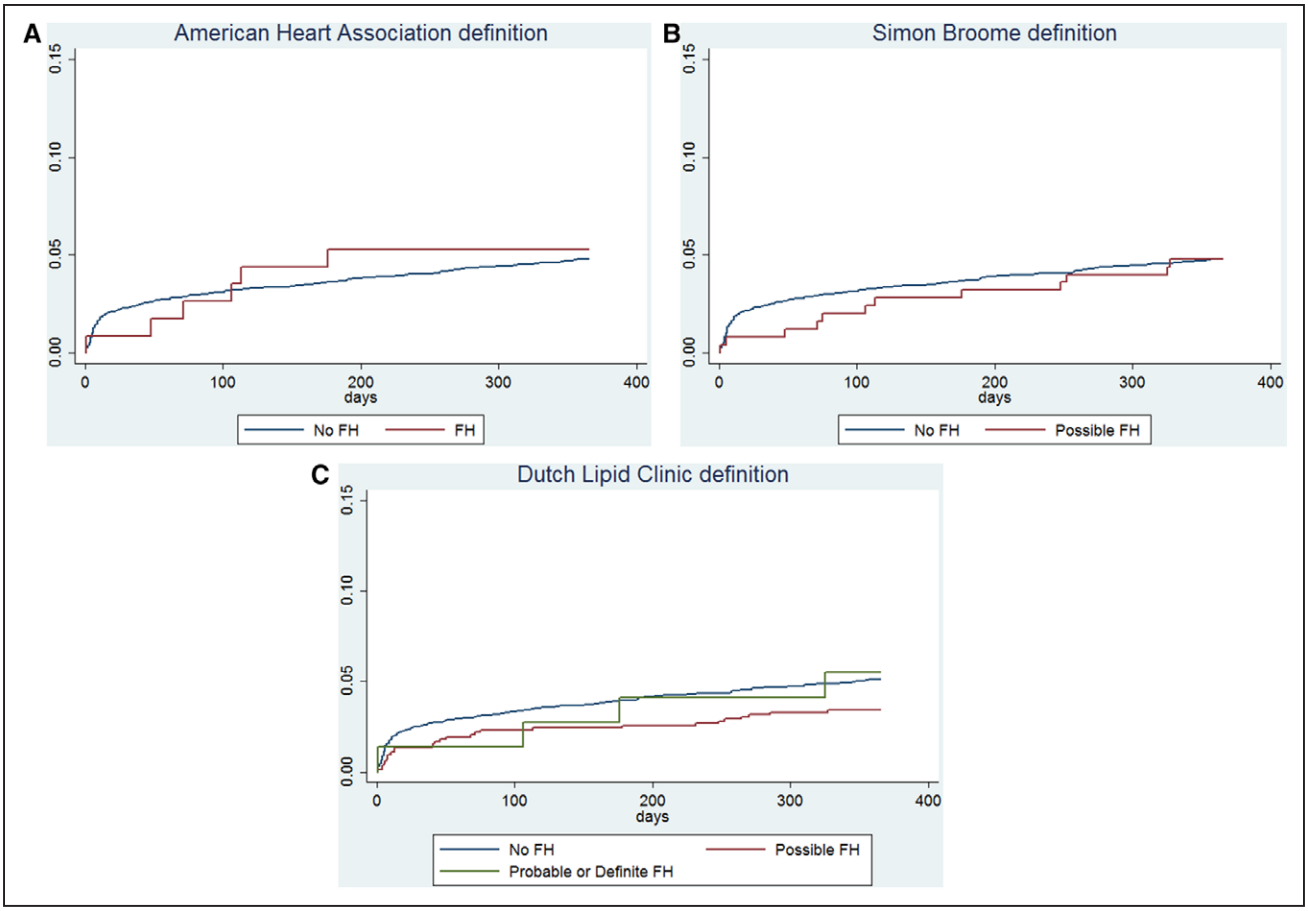


**Figure 1. Incidence of recurrent coronary events after acute coronary syndrome by presence of familial hypercholesterolemia (FH; n=4534).**

**A**, American Heart Association definition of FH. **B**, Simon Broome Register definition of FH. **C**, Dutch Lipid Clinic definition of FH.

cohorts from the general population, but none prospectively compared the recurrence of cardiovascular events after CHD in patients with or without FH, nor did they adjust the prognosis of FH according to cardiovascular risk factors and severity of CHD. The Simon Broome Register Group reported mortality rates of patients with FH.[18–20] These studies were conducted mainly in primary prevention, and ≈70% of men and 80% of women had no pre-existing CHD at the beginning of follow-up. However, the benefit of statins may differ between primary and secondary prevention among patients with FH.[20] Furthermore, recommendations for clinical management of patients with FH and CHD should also be based on the recurrence of nonfatal clinical events. One study carried out in Dutch lipid clinics prospectively examined the rates of coronary events in patients with FH without a record of pre-existing cardiovascular disease.[9] Other studies in Dutch lipid clinics were retrospective or cross-sectional, and cardiovascular risk estimates may have been prone to confounding biases.[14,21] One prospective study in a single lipid clinic in the Netherlands examined the risk of recurrence of cardiovascular events in 131 patients with FH and pre-existing CHD who were treated with statins.[10] However, they did not adjust recurrence estimates to cardiovascular risk factors, statin dose, or severity of CHD. To the best of our knowledge, our study is the first to prospectively assess the risk of coronary and cardiovascular event rates in a large cohort of patients with FH after ACS who were treated with high-intensity statins.

Despite wide implementation of high-dose statins after ACS, patients with FH remain at increased risk of recurrence compared with patients without FH after accounting for age. In clinical practice, the implementation of a systematic screening strategy for FH is limited by the costs of genetic testing and counseling.[22] Because cardiovascular risk was shown to be driven by both phenotype and genotype,[21,23] expert groups proposed simplified definitions for establishing a diagnosis of FH based on clinical criteria.[1–3] In our study, we were able to demonstrate how these simplified screening algorithms using cholesterol levels and family or personal history of premature CHD as diagnostic criteria were powerful and efficient tools to identify FH in patients with ACS at high risk of coronary event recurrence despite high-intensity statin treatments. Furthermore, treatments other than lipid-lowering drugs such as dual antiplatelet therapy

**Table 3. Comparison of Clinical Management After ACS Between Patients With and Without FH by Definition (n=4534)**

| | No FH | AHA FH | Simon Broome Possible FH | Dutch Lipid Clinic Possible FH (3–5 Points) | Dutch Lipid Clinic Probable/Definite FH (>5 Points) |
|---|---|---|---|---|---|
| n | 3,589 | 114 | 250 | 825 | 73 |
| Acute revascularization (n=4498), n (%) | | | | | |
| PCI | 3186 (89.5) | 106 (93.0) | 232 (93.2) | 757 (92.4) | 63 (86.3) |
| CABG | 91 (2.6) | 1 (0.9) | 1 (0.4) | 13 (1.6) | 0 (0.0) |
| Lipid-lowering drugs at discharge (n=4481), n (%) | | | | | |
| Statins | 3,456 (97.6) | 112 (99.1) | 245 (98.4) | 811 (98.9) | 69 (94.5) |
| High-dose statins* | 2,383 (67.3) | 93 (82.3) | 202 (81.1) | 633 (77.2) | 54 (74.0) |
| Other lipid-lowering agents† | 53 (1.5) | 8 (7.1) | 12 (4.8) | 18 (2.2) | 7 (9.6) |
| Secondary prevention, n (%) | | | | | |
| Cardiac rehabilitation (n=4482) | 2,258 (63.8) | 90 (79.6) | 195 (78.3) | 626 (76.2) | 57 (78.1) |
| $P2Y_{12}$ inhibitors (n=3821)‡ | 2,887 (96.4) | 98 (99.0) | 221 (99.1) | 707 (97.4) | 61 (100) |
| Lipid-lowering drugs at 1 y (n=4204), n (%) | | | | | |
| Statins | 3,083 (93.2) | 102 (93.6) | 223 (94.9) | 739 (94.0) | 67 (94.4) |
| High-dose statins* | 1,856 (56.1) | 77 (70.6) | 167 (71.1) | 501 (63.7) | 50 (70.4) |
| Other lipid-lowering agents† | 143 (4.3) | 17 (15.6) | 37 (15.7) | 69 (8.8) | 14 (19.7) |
| Lipid values at 1 y (n=2345) | | | | | |
| LDL cholesterol, mean (SD), mg/dL | 82.9 (31.3) | 119.4 (45.9) | 112.3 (39.9) | 93.7 (35.0) | 125.5 (46.8) |
| LDL ≤70 mg/dL, n (%) | 687 (37.7) | 5 (8.8) | 13 (9.8) | 101 (22.5) | 2 (4.5) |
| LDL ≤100 mg/dL, n (%) | 1,375 (75.4) | 28 (49.1) | 62 (47.0) | 299 (66.7) | 16 (36.4) |

ACS indicates acute coronary syndrome; AHA, American Heart Association; CABG, coronary artery bypass graft; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; and PCI, percutaneous coronary intervention.

*High-dose statins included atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg.

†Lipid-lowering agents other than statins included fibrates, niacin, ezetimibe, and bile acid resins.

‡Prescription of clopidogrel, prasugrel, or ticagrelor in addition to aspirin after PCI with a stent.

were prescribed more often in patients with FH than in those without FH. Patients with FH also had better coronary flow after percutaneous coronary intervention than patients without FH. Overall, these factors may have led to underestimation of the risk ratios we reported.

We also reported that additional adjustment with baseline LDL cholesterol at the time of ACS did not further reduce the risk gap between patients with and without FH. From these results, we propose that the elevated cardiovascular risk in ACS patient with FH may be explained by lifelong persistence of elevated LDL cholesterol levels, as well as familial susceptibility to atherosclerosis.

Novel lipid-lowering drugs such as proprotein convertase subtilisin kexin 9 inhibitors are anticipated to further reduce the risk of cardiovascular disease in patients with heterozygous FH, in whom low levels of LDL cholesterol cannot be achieved with statins only.[24,25] However, in light of the high cost of proprotein convertase subtilisin kexin 9 inhibitors, prescription strategies for these drugs will need to target specifically those adults most likely benefit from intensified lipid management such as patients with FH.[26] The benefit of systematically identifying patients with FH at the time of hospitalization for ACS to reduce the recurrence of cardiovascular events still needs to be demonstrated. Nevertheless, FH is a frequent disorder among patients with ACS, with prevalence rates reaching 15% in some studies.[5,6,27,28] Systematic screening for FH based on clinical criteria has been shown to be easy to carry out and affordable. With the added benefits that proprotein convertase subtilisin kexin 9 inhibitors are expected to bring in terms of cardiovascular events reduction, systematic screening for FH should be encouraged in patients with ACS until further evidence is available.

Our study has strengths and limitations. Our results have strong external validity because our study population was derived from nonselected patients with ACS in 4 different centers, in contrast to previous studies that were conducted mainly in lipid clinics.[10,14,18,19] However, the increased recurrence risk of coronary events

**Table 4. Risks of Recurrent Events in Young Patients With Premature ACS With Respect to Presence of FH (n=1369)**

| | AHA Definition | | Simon Broome Definition | | Dutch Lipid Clinic Definition | | |
|---|---|---|---|---|---|---|---|
| | No FH | FH | No FH | Possible FH | No FH (Score <3) | Possible FH (Score 3–5) | Probable/ Definite FH (Score >5) |
| Coronary events | | | | | | | |
| Events/participants, n | 31/1307 | 4/62 | 25/1172 | 10/197 | 11/644 | 20/660 | 4/65 |
| Incidence rate, per 100 person-y | 2.4 | 6.9 | 2.2 | 5.3 | 1.7 | 3.1 | 6.4 |
| Unadjusted HR (95% CI) | 1.00 (Referent) | 2.78 (0.98–7.88) | 1.00 (Referent) | 2.39 (1.15–4.99) | 1.00 (Referent) | 1.78 (0.86–3.72) | 3.66 (1.17–11.50) |
| Age/sex–adjusted HR (95% CI) | 1.00 (Referent) | 3.02 (1.06–8.57) | 1.00 (Referent) | 2.54 (1.22–5.29) | 1.00 (Referent) | 1.86 (0.89–3.88) | 3.85 (1.23–12.12) |
| Multivariable-adjusted HR (95% CI; n=1283)* | 1.00 (Referent) | 2.95 (1.03–8.49) | 1.00 (Referent) | 2.72 (1.29–5.75) | 1.00 (Referent) | 1.59 (0.74–3.38) | 3.71 (1.16–11.81) |
| Cardiovascular events | | | | | | | |
| Events/participants, n | 41/1307 | 4/62 | 33/1172 | 12/197 | 16/644 | 25/660 | 4/65 |
| Incidence rate, per 100 person-y | 3.2 | 6.9 | 2.9 | 6.4 | 2.6 | 3.9 | 6.4 |
| Unadjusted HR (95% CI) | 1.00 (Referent) | 2.09 (0.75–5.84) | 1.00 (Referent) | 2.18 (1.13–4.22) | 1.00 (Referent) | 1.54 (0.82–2.88) | 2.51 (0.84–7.50) |
| Age/sex–adjusted HR (95% CI) | 1.00 (Referent) | 2.24 (0.80–6.26) | 1.00 (Referent) | 2.29 (1.18–4.43) | 1.00 (Referent) | 1.59 (0.85–2.98) | 2.63 (0.88–7.88) |
| Multivariable-adjusted HR (95% CI; n=1283)* | 1.00 (Referent) | 2.16 (0.76–6.13) | 1.00 (Referent) | 2.44 (1.24–4.79) | 1.00 (Referent) | 1.42 (0.74–2.71) | 2.66 (0.87–8.12) |

AHA indicates American Heart Association; CI, confidence interval; FH, familial hypercholesterolemia; and HR, hazard ratio.

*Adjusted for age, sex and cardiovascular risk factors, including body mass index, current smoking, hypertension, diabetes mellitus, pre-existing cardiovascular disease, high-intensity statins at discharge, attendance to cardiac rehabilitation at discharge, and results of the 6-months GRACE (Global Registry of Acute Coronary Events) risk score.



applies only to patients with ACS with FH. Despite the fact that we adjusted our estimate to the severity of ACS, selection bias of patients with FH who have some unmeasured confounder leading them to be hospitalized at varying rates than patients without FH also is possible.[29] We were not able to assess the concordance of the rates of FH measured according to the clinical definitions we chose for its diagnosis with the results of genetic testing for FH. Because clinical criteria without molecular diagnosis may overestimate the prevalence of FH, many of our patients classified as having FH may in fact have polygenic hypercholesterolemia.[23,30] This misclassification could, in turn, have underestimated the cardiovascular risk of patients classified as FH, as suggested by the greater risk ratio associated with FH compared with polygenic hypercholesterolemia in the probable/definite category of the Dutch Lipid Clinic definition. In other words, patients with a confirmed genetic diagnosis of FH may be at even greater risk of cardiovascular events than what we found in our study. Furthermore, we did not collect data on family history of high LDL cholesterol levels or on skin manifestations such as xanthoma. Overall, these missing data decreased the sensitivity of the Simon Broome and the Dutch Lipid Clinic definitions. On the other hand, we found a consistent association between FH and cardiovascular events across all 3 clinical definitions for FH.[31] Also of note is that LDL cholesterol levels are lowered 12 to 24 hours after an ACS, another cause that could have led to the prevalence of FH being underestimated in our study.[32,33] This potential misclassification of FH may, in turn, have decreased the relative incremental risk associated with FH. Finally, we used self-reported information on family history of premature CHD, and a recall bias may have occurred in patients with ACS, leading to an overestimation of FH prevalence. However, recent data presented by others showed similar reporting accuracy of family history in patients with and without pre-existing cardiovascular disease.[34]

## CONCLUSIONS

Patients with FH hospitalized for ACS are at high risk of coronary event recurrence after discharge despite the

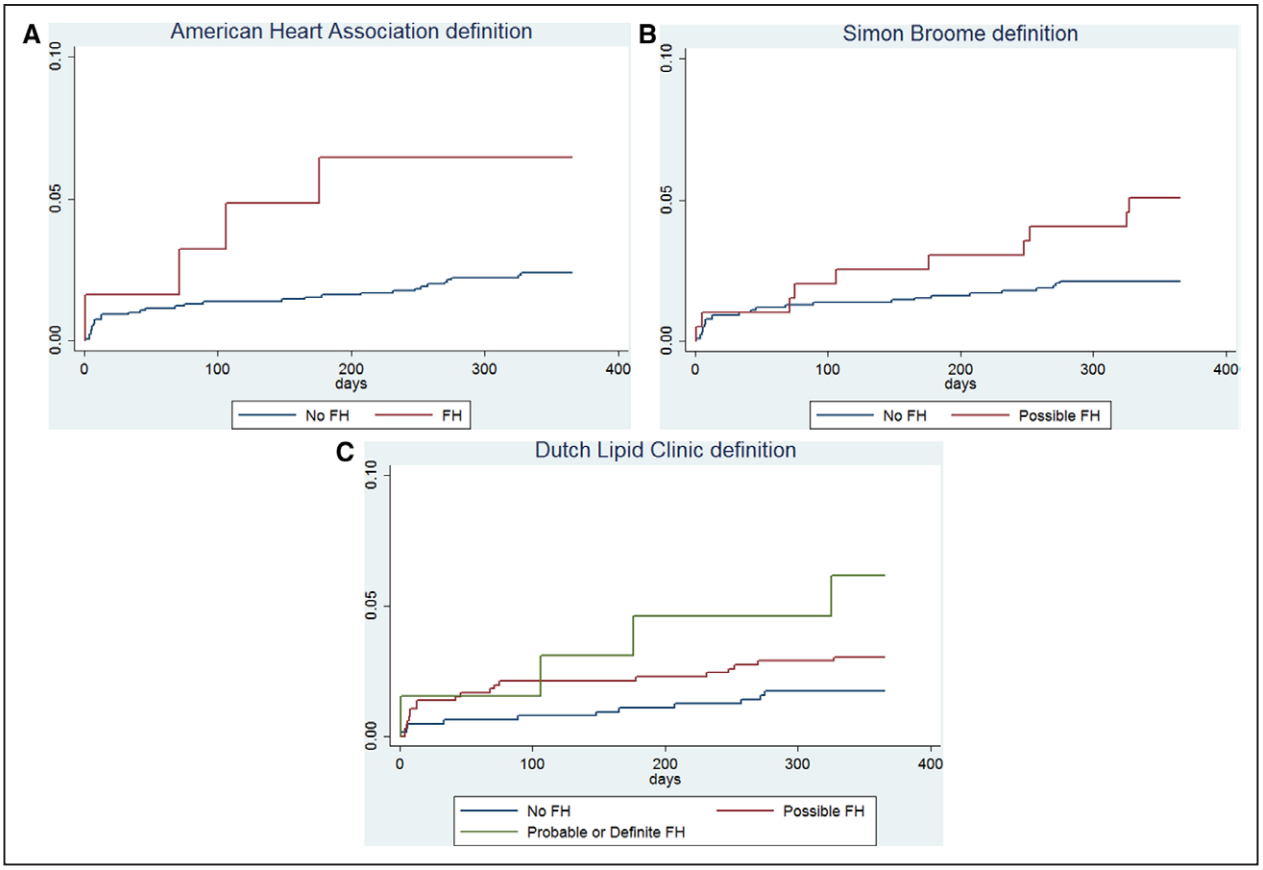


**Figure 2. Incidence of recurrent coronary events in young patients with premature coronary heart disease by presence of familial hypercholesterolemia (FH; n=1369).**
**A**, American Heart Association definition of FH. **B**, Simon Broome Register definition of FH. **C**, Dutch Lipid Clinic definition of FH.

use of high-dose statins. In the era of systematic prescription of high-dose statins, measuring cholesterol levels at the time of ACS diagnosis has been considered superfluous. On the other hand, our results suggest that patients with FH need to be identified because they are less likely to reach target LDL cholesterol levels. Proper identification of patients with FH will also be useful for testing new approaches in individualized treatment such as novel lipid-lowering drugs, family counseling, and tailored secondary prevention. Finally, the intensification of lipid management and secondary prevention in patients with FH may reduce the recurrence of cardiovascular events.

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## DISCLOSURES

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## FOOTNOTES

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# Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes

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**SUPPLEMENTAL MATERIAL (Online data supplement)**

**for "Prognosis of patients with familial hypercholesterolemia after acute coronary syndrome"**

David Nanchen et al.

**Supplemental Tables**

**Table 1**

American Heart Association criteria for clinical diagnosis of familial hypercholesterolemia (FH) (n=4,534)

| LDL-cholesterol >4.9 mmol/l<br>AND | **Grading** | **% subject scoring (number)** |
|---|---|---|
| First degree relative with known premature coronary heart disease (< 55 years men; < 60 years women) | FH | 2.5 (114) |
| First-degree relative with LDL-cholesterol > 4.9 mmol/l | FH | NA |

NA, not available

**Table 2**

Simon Broome Register criteria adapted from NICE guidelines for diagnosis of familial hypercholesterolemia (FH) (n=4,534)

| Total cholesterol > 7.5 mmol/l OR LDL-cholesterol >4.9 mmol/l AND | **Grading** | **% subject scoring (number)** |
|---|---|---|
| First degree relative with known premature coronary heart disease (< 55 years men; < 60 years women) | Possible FH | 2.6 (118) |
| Personal history of premature coronary heart disease (< 55 years men; < 60 years women) | Possible FH | 4.3 (197) |
| Tendon xanthomas | Definite FH | NA |
| DNA mutation | Definite FH | NA |

NA, not available

**Table 3**

Dutch Lipid Clinic Network criteria for diagnosis of familial hypercholesterolemia (FH)

(n=4,534)

| **Variable** | **Grading** | **% subject scoring (number)** |
|---|---|---|
| First degree relative with known premature atherosclerosis OR with known LDL-cholesterol > 95$^{th}$ percentile, OR personal history of premature (< 55 years men; < 60 years women) cerebral or peripheral vascular disease, OR LDL-cholesterol 4.0-4.9 mmol/l* | 1 point | 37.3 (1,691) |
| Personal history of premature (< 55 years men; < 60 years women) coronary heart disease OR first-degree relative with tendon xanthomata and/or arcus cornealis OR first-degree relative child below 18 years with LDL-cholesterol > 95$^{th}$ percentile OR | 2 points | 30.2 ( 1,369 ) |
| LDL-cholesterol 5.0-6.4 mmol/l* | 3 points | 5.8 (261) |
| Presence of arcus cornealis below 45 years | 4 points | NA |
| LDL-cholesterol 6.5-8.4 mmol/l* | 5 points | 1.0 (45) |
| Presence of tendon xanthomata | 6 points | NA |
| LDL-cholesterol > 8.5 mmol/l* OR functional mutation in LDL receptor gene present | 8 points | 0.09 (4) |

NA, not available

*Only in those with triglyceride levels < 2.3 mmol/l

Possible FH: 3-5 points; probable FH: 6-7 points; definite FH >= 8 points

**Table 4** – Risks of recurrent events after acute coronary syndrome (ACS), with respect to presence of familial hypercholesterolemia (FH) in patient not using lipid-lowering drugs at admission (n=3,234)

| | **AHA definition** | | **Simon Broome definition** | | **Dutch Lipid Clinic definition** | | |
|---|---|---|---|---|---|---|---|
| | **No FH** | **FH** | **No FH** | **Possible FH** | **No FH** (score <3) | **Possible FH** (score 3-5) | **Probable/definite FH** (score > 5) |
| **Coronary events** | | | | | | | |
| Number of events/participants | 125/3,163 | 4/71 | 122/3,067 | 7/167 | 109/2,555 | 18/637 | 2/42 |
| Age sex adjusted HR (95% CI) | 1.00 (ref) | 2.02 (0.74;5.51) | 1.00 (ref) | 1.92 (0.87;4.23) | 1.00 (ref) | 1.30 (0.75; 2.25) | 2.56 (0.61;10.65) |
| Multivariable-adjusted HR (95% CI)[1] (n= 1,283) | 1.00 (ref) | 2.97 (1.07;8.27) | 1.00 (ref) | 2.70 (1.19;6.12) | 1.00 (ref) | 1.30 (0.69;2.47) | 3.21 (0.75;13.68) |
| **Cardiovascular events** | | | | | | | |
| Number of events/participants | 161/3,163 | 5/71 | 157/3,067 | 9/167 | 143/2,555 | 21/637 | 2/42 |
| Age sex adjusted HR (95% CI) | 1.00 (ref) | 1.89 (0.77;4.63) | 1.00 (ref) | 1.82 (0.91;3.65) | 1.00 (ref) | 1.07 (0.64; 1.74) | 1.73 (0.42;7.15) |
| Multivariable-adjusted HR (95% CI)[1] (n= 2,993) | 1.00 (ref) | 1.98 (0.72;5.44) | 1.00 (ref) | 2.05 (0.97;4.35) | 1.00 (ref) | 1.01 (0.57; 1.79) | 2.01 (0.48;8.42) |

[1]Adjusted for age, sex and cardiovascular risk factors, including body mass index, current smoking, hypertension, diabetes mellitus, pre-existing cardiovascular disease, high-intensity statins at discharge, attendance to cardiac rehabilitation at discharge, and results of the 6-months GRACE risk score.

Abbreviations: AHA, American Heart Association ; HR, hazard ratio; CI, confidence interval; GRACE, Global Registry of Acute Coronary Events

Carolyn: Welcome to Circulation On The Run, your weekly podcast, summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Nam, associate editor from the national heart center and Duke National University of Singapore.

In just a while, we will be discussing patients with familial hypercholesterolemia after acute coronary syndrome, and the new data in this week's issue that suggests we still need to pay special attention to this group of patients even in the current era of the widespread use of high intensity satins. First here's your summary of this weeks issue.

The first paper suggests that we may need to look at thyroid function in our risk assessment sudden cardiac death in the general population. This paper is from co primary authors Dr. Chacker in Van Der Burgh and corresponding author Dr. Strecker and colleagues from the Erasmus University medical center in water dom.

The authors studied the association of thyroid function with sudden cardiac death in more than 10,000 participants of the population based Water Dom study. They found the higher levels of 3T4 were associated with an increased risk of sudden cardiac death even in the normal range of thyroid function. The estimated hazard ratio was 2.28 per one nano-gram per deciliter of 3T4, and these risk estimates did not change substantially even after stratification by age or sex or sensitivity analysis excluding participants with an abnormal 3T4. The absolute 10 year risk of sudden cardiac death increased in youth thyroid participants from 1 to 4% within increasing 3T4 levels.

Thus this study suggests that 3T4 and additive marker in risk stratifications for sudden cardiac death in the general population. Further research is needed to assess the possible additional benefit of using 3T4 levels to re stratify and prevent sudden cardiac death.

The next study reminds us that therapies to reduce ischemic events in patients undergoing percutaneous coronary intervention are still really important even in the current era of changing definitions of periprocedural myocardial infarction. This study is from first author Dr. Cavender of University of North Carolina chapel hill and corresponding author Dr. Bach Brigham women's hospital and colleagues.

The authors looked at more than 11,000 patients randomized to cangrelor or clopidogrel int the champion phoenix trial.

Cangrelor is an intravenous P2Y-12 inhibitor approved to reduce periprocedural ischemic events in patients undergoing percutaneous coronary intervention who are not pretreated with with a P2Y-12 inhibitor.

The authors explored the effects of cangrelor on myocardial infarction using different definitions of myocardial infarction and perform sensitivity analysis on primary endpoint.

They found that 4.2 percent of patients had a myocardial infarction defined by the second universal definition within 48 hours after undergoing PCI. When the sky

definition of periprocedural MI was used, there were fewer total myocardial infarction, but the effects of cangrelor remain significant.

Finally similar effects were seen when MI's were restricted to those defined with large bio marker elevations or by symptoms of ECG changes. Very importantly patients who had an MI regardless of the definition, were at increased risk of death at 30 days.

In summary changes in the definition of MI used in the primary endpoint did not affect the overall findings from the champion phoenix trial. This study also reminds us that periprocedural MI remains an important clinical event in the current era. Being associated with increased risks of death at 30 days, and therefore reducing ischemic events in patients undergoing PCI remains very important.

The final paper describes experimental evidence of a novel treatment approach to hypertension using micro RNA's. This paper is from first author Dr. Lee and corresponding authors Dr. Chinn and Wang from Tong G medical college and Whadrom University of Science and Technology in Wuhan China.

Micro RNA's are a class of small non-coding RNA's that regulate gene expression at a post transcriptional level. These authors compared the expression of key neucler genoman coded and mitochondrial genoman coded genes involved reactive oxygen species production in spontaneous hypertensive rats and wistar rats. They then used bioinformatics to predict the micro RNA targets followed by biochemical validation using real time PCR and immunial precipitation.

They first found that there was down regulation of mitochondrial DNA encoded sitoca B in the spontaneous hyper intensive rats, which appeared to directly contribute to the increased mitochondrial reactive oxygen species.

Next they found that mere 21 a key micro RNA induced into hyper spontaneous rats, was able to trans-locate into mitochondria to counteract the mitochondria pseudonym B down regulation. Finally, they showed that exogenous mere 21 delivered by recombinant adeno associated virus was able to lower blood pressure and attenuate cardiac hypertrophy in the spontaneously hypertensive rat model.

These findings are striking because they provide experimental support for developing micro RNA based treatments for hypertension.

Those were your summaries of original papers but before I go, I just have to highlight this in depth review paper in this week's issue, and it is regarding sodium glucose co transported to inhibitors or SLG2 inhibitors in the treatment of diabetes, discussing the cardiovascular and kidney affects potential mechanisms and clinical applications.

It is a beautiful review article written by first author Dr. Heresphink of the University Medical Center Groningen, corresponding author Dr. Churney from Toronto general hospital and colleagues. Truly a must read, but now here is our featured paper.

Our featured paper today is on patients with familial hypercholesterolemia after acute cornery syndromes. Today I have with us the first and corresponding author David Nan chin university of Lausanne in Switzerland.

Hi David, thanks for joining us.

David: Hi, I'm very happy to be here.

Carolyn: As the associate editor who managed this paper we have Dr. Amat Kira and you will recognise him as the digital strategies editor as well from UT Southwestern. Welcome back Amat.

Amat: Thank You Carolyn, happy to be here.

Carolyn: I am really curious about this paper because it speaks of familial hypercholesterolemia that most of us would assume is very rare.

Now David, I know that you actually published prevalence in a prior paper last year, but could you maybe start by telling us why we should, how common is this in our patients with acute coronary syndrome?

David: In fact we studied patients who is hospitalized with acute coronary syndrome in several university hospitals in Switzerland. Of course we try our best to include all classifications in the study in order to be very protective of the acute coronary syndrome population.

We found that among patients with acute coronary syndrome, familial hypercholesterolemia was not a rare disease. We found a prevalence of 2-5% which is in fact 10 times higher than what is thought to be in the general population.

The important point here is that we use very simple clinical catatonia to assist the prevalence of adage. This catatonia includes unbelievable[inaudible 00:08:50] and the family of Bethany of coronary heart disease. This criteria are very easy to use and implement in a clinical practice in the sitting in acute coronary syndrome to detect patients with familial hypercholesterolemia.

Carolyn: Exactly. You did not use molecular diagnosis in your paper, but yet, with these simple criteria there was a very important clinical take home message. Could you tell us about those findings?

David: The question we wanted to answer here is wanted to know what happened to this patient with familial hypercholesterolemia after hospital discharge. We found that patients with familial hypercholesterolemia were an increased risk of recurrence of cornea events within the year after discharge, and this is despite the use of idol science.

In fact, one year after the coronary syndrome, 7 people found a patient with adage were still using idle studies, which is very good we were quite impressed by these numbers, but they mean[inaudible 00:09:57] one year after the acute coronary syndrome, with

one in twenty become affected later.

Most of these patients were not able to decrease their added cholesterol to lower evens.

I really think there is clear room for infestation of leamington therapy among these patients. In any of those drugs available from my seeing and very effective to decrease and [inaudible 00:10:25] to substance, but they are very expensive.

Maybe the best initial strategy, to prescot these drugs, is to target patients with familial hypercholesterolemia after acute coronary syndrome. Because these patients are at high risk of recurrence and most of them cannot achieve their cholesterol level with our studies.

Carolyn: Congratulations for being really the first to show that. This is common and it affects recurrent events. I think actually the first step is to recognize this in our patients which very few of us really do I think.

Amat from your point of view, knowing the results of this paper how has it changed your clinical practice?

Amat: Absolutely Carolyn. First I congratulate Dr. Nan chin and his colleagues. This was an incredibly important paper, and I think as you pointed out, one of the first to really show us why it is irrelevant to show us why it is relevant to identify FH at the time of an ACS.

Generally even when I work with my trainees when we talk about FH, everyone is thinking, "Well, we'll just put everyone on statins," and it's well appreciated. We can think about cascades swinging and why it's important to their offspring, but what Dr. Nan chin and his colleagues have certainly highlighted, is that these patients are at higher risks for recurrent ACS and recurrent events, and that's incredibly important as mentioned that tells us that maybe the routine treatment post ACS with high dose statins is not sufficient.

What's next is the tricky part, do we initiate PCS canine initially, do we add a zedemi upfront. Sort of the next step is the part that's a little bit more tricky, but I certainly see a potential for augmented therapy in these patients up front.

Carolyn: I like the way you said tricky, and that's usually when we call for an editorial isn't it?

Amat: That is correct as we will see with this article.

Carolyn: I really like the title of it, "Diagnosis and Management of Petra Zygas familial hypercholesterolemia too little and too late."

That was very interesting, but are there any other take home messages from your end David?

David: Maybe one thing we can add ... We are currently trying to change our practice regarding these reasons that we have now. We have now implemented in our casualty department a system that's explaining strategy to identify this patient, to identify patient with asage.

We have a prevention team that can provide very early during hospitalization additional information for this patient about asage. That's one very important point is to encourage family testing especially for the children of the patient and also to provide concerning for other cardiovascular risk factors. Because we also found that half of these patients with asage were smokers in fact and 40% of them had hypertension.

Certainly to address the other cardio risk factor in patients with asage so certainly very important. At the end part of what we are doing is we are assured of the patient will an appropriate medical follow up in the primary care setting because it's also very important for management of asage and circular prevention in the primary care setting after discharge.

Carolyn: Wow. Those are excellent points. Very practical advice on screening, management, and really just applying the results of what you found. Congratulations once again.

Amat I'm going to switch tracks a little bit now. Since we've got you online I really have to ask you a couple of things with your hat as a digital strategies editor.

Has it been two months since we first chatted even about this podcast which is part of the digital strategies. Let's take stock of it. How are things going?

Amat: Well, so far I think excellent and frankly one of the highlights of our digital strategies is your podcast. It's gotten rave reviews and certainly appreciate all your enthusiasm and your unique take on how to do this. We've also had some excellent work with our social media. We have a revised website which has a lot more real estate for some novel offerings, and I think we certainly can't rule out traditional print media, but those articles that come out online.

It's been really an exciting time and thinking of novel ways to share new information in a modern era.

Carolyn: Right. Thanks to you really Amat and I would really want to bring out one of the strategies that we may have not talked about so often yet, and that's the "on my mind" vlogs.

The reason I'm going to bring it up is because last week I was struck by the on my mind article by Milton Packer and it's entitled, "Heart Failure's Dark Secret. Does anyone really care about optimal medical therapy?" That's just awesome. Could you tell us a bit more about this vlog.

Amat: I think you hit the nail on the head there it certainly an edgy and controversial title, and if you think about it that's the purpose of this in most of our academic writing. It's a little

bit stiff in following certain para dines, and more formal para view. The purpose here for the on my mind was literally that for someone who is a thought leader to free associate various ideas they have that would be controversial or edgy or may not be accepted down the main stream.

That's a bit on purpose because we hope to create a dialog around that. If you look on our webpage, there's actually a place where people can add comments or start a dialog saying whether they agree or disagree, or begin an important conversation around these edgy topics.

Carolyn: I think that's the really cool part when we can actually start interacting with our readers and listeners online that way.

Thank you to my wonderful guests and thank you listeners for listening this week. Don't forget to tune in next week for more highlights and features.