with cirrhosis of other aetiologies (COE). The authors point to the absence of patients with alcoholic liver disease (ALD) among patients with COE in our study [2]. Indeed, our study differed in its primary goal and selected population from their recent publication [3] that demonstrated a high prevalence of coronary artery disease among patients with predominantly alcoholic cirrhosis. The primary objective of our study was to evaluate the relationship between NASH-related cirrhosis and coronary artery disease (CAD), compared with other aetiologies of cirrhosis, in a population that had undergone liver transplantation. The selection bias in our age and sex-matched COE group, comprised of only patients with viral hepatitis and cholestatic liver disease, reflects the leading causes of liver cirrhosis in patients undergoing liver transplantation at our center. "Pure" alcoholic cirrhosis is an unusual indication for liver transplantation at our center, although in a significant number of patients with hepatitis C, alcohol is considered a contributing factor to the development of cirrhosis.

The data discussed in the letter by Kalaitzakis and Björnsson confirms a high prevalence of CAD in patients with NASH-related cirrhosis compared to cirrhosis secondary to other causes (excluding ALD) which supports our observations [2]. However, their finding of a high prevalence of CAD in ALD-cirrhosis is interesting and unexpected, given the results of previous autopsy studies [4,5] and the protective effect of moderate alcohol consumption on atherosclerosis suggested by many other studies [6,7]. In their study population [1,3] the incidence of important risk factors for CAD including age, smoking, male gender, hypertension and diabetes were higher in ALD-cirrhosis compared to their COE group. These findings not only point to the consistent importance of cardiovascular risk factors in determining the risk of CAD in a group (ALD) conventionally considered to be protected from CAD, but also raise the important question of the relative contribution of alcohol and metabolic factors in the pathogenesis of cirrhosis in their patients etiologically classified as ALD.

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HCV genotype 3: An independent predictor of fibrosis progression in chronic hepatitis C

To the Editor:

The multi-centre study, by Bochud et al. [1], demonstrating an association between hepatitis C virus (HCV) genotype 3 and rapid progression of liver fibrosis in chronically infected patients, amplifies the potential clinical meaning of HCV genotypes, originally identified as predictors of interferon therapy outcome. The report from Switzerland corroborates the increasing evidence that the natural history of hepatitis C may be also influenced by the genotype of HCV in addition to host and environmental co-factors of morbidities. The road to HCV genotype being a modifier of the course of HCV infection was opened a long time ago by HCV-1, shown to be associated with rapid progression of recurrent hepatitis C in liver transplanted patients [2], and with increased risk of hepatocellular carcinoma (HCC) in patients with cirrhosis [3], and by HCV-2 associated with ALT flares that ultimately accelerate the course of chronic hepatitis in untreated patients [4]. In this context, the paper by Bochud et al. adds nicely to these find-

Table 1
Baseline and clinical characteristics of the 327 patients.

Patients	Overall ($n = 327$)	HCV-1 ($n = 143$)	HCV-2 ($n = 104$)	HCV-3 ($n = 80$)	p^a
Male gender	192 (58%)	75 (52%)	49 (47%)	53 (66%)	0.03
Median age at biopsy (years)	47	48	53	42.5	<0.001
Median age at infection (years)	21	21	24	19	0.09
Median infection duration (years)	23	25	24.5	20	0.001
HCV genotype					
1	143 (43%)	–	–	–	
2	104 (31%)	–	–	–	
3	80 (24%)	–	–	–	
HCV reported risks					<0.001
IVDA[b]	94 (29%)	25 (17%)	5 (4%)	64 (81%)	
Transfusion	228 (69%)	117 (81%)	99 (95%)	12 (13%)	
Others	5 (1%)	1 (0%)	1 (0%)	4 (5%)	
Biopsy fibrosis stage (Ishak)					0.01
0	6 (1%)	5 (3%)	1 (0%)	0 (0%)	
1	85 (26%)	32 (22%)	36 (34%)	17 (21%)	
2	102 (31%)	38 (22%)	39 (37%)	25 (31%)	
3	44 (13%)	17 (12%)	12 (11%)	15 (18%)	
4	26 (8%)	13 (9%)	4 (4%)	9 (11%)	
5	28 (8%)	17 (12%)	7 (7%)	4 (5%)	
6	36 (11%)	21 (15%)	5 (5%)	10 (12%)	

[a] Categorical values were compared using a chi-square test and continuous variables were compared using a median test.
[b] IVDA, intra-venous drug abuse.

ings, as it shows HCV-3 to be associated with an accelerated deposition of fibrosis in the liver.

To externally validate these findings we assessed a cohort of patients prospectively followed at our centre between December 2008 and May 2009. Of the 3566 patients with chronic HCV infection consecutively admitted to our centre for biochemical and clinical evaluation, 327 (9%) knew the date of infection and had undergone at least one liver biopsy before any antiviral treatment. All liver biopsy specimens were considered adequate for fibrosis assessment [5]. Fibrosis was quantified by the Ishak staging system, with scores ranging from 0, representing no fibrosis to 6 representing cirrhosis [6].

At variance with the study population described by Bochud et al. where the majority of patients acquired HCV through intra-venous drug abuse (IVDA), two-thirds of our patients with the known data of infection identified blood transfusions as the relevant risk factor for HCV infection (Table 1). Compared to Bochud's study, our patients were slightly older (median age at biopsy 47 vs. 42 years) while they had a comparable duration of HCV infection in years (23 vs. 21 years). Consistent with Bochud's observation, we noticed a faster progression of liver fibrosis in HCV-3 patients. Among the 327 patients of our cohort 134 (41%) developed a significant degree of fibrosis, defined as an Ishak staging score $\geqslant 3$. While the proportion of patients developing a significant fibrosis was not influenced by

HCV genotype (HCV-1: 68/143, 48%; HCV-2: 28/104, 27%; HCV-3: 38/80, 47%), when comparing the mean disease duration in these patients significant differences emerged. In fact, the mean time lag necessary to develop a significant fibrosis was 28.3 years for HCV-1, 24.2 years for HCV-2 patients and 21.8 years for HCV-3 infected patients ($p = 0.03$). We omitted to calculate the pace of fibrosis progression in units per year since we think that it is intrinsically flawed, as the authors correctly point out, since not only it assumes that fibrosis progression is constant over time, a finding that has been proven incorrect [7], but also it transforms a qualitative variable, such as the pattern of fibrosis deposition in the liver, into a quantitative variable [8].

The demonstration that HCV-3 genotype is a relevant modifier of the natural history of chronic infection further supports anticipated treatment of these patients, whenever possible.

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