SUPPLEMENTARY MATERIAL #1

IMPACT OF STATINS ON FIB-4 PREDICTIONS: DETERMINING THE INDICATION FOR STATIN

The indication for a statin was determined according to the Canadian cardiovascular society were statins are indicated to any patients with clinical atherosclerosis, abdominal aortic aneurysm, Chronic kidney disease (age ≥ 50 years) where eGFR <60 mL/min/1.73 m2 or albumin to creatinine ratio > 3 mg/mmol and diabetes mellitus when patients age is >= 40 or they have been diabetic for 15 years or more in case with type 1 diabetes mellitus [1].

In addition, for primary prevention of cardiovascular disease, statin is indicated in all patients who have Framingham risk score (FRS) suggesting a 10-year cardiovascular disease risk of >20% and to some patients with intermediate 10 years cardiovascular risk (10-19%) (those with LDL-C >= 3.5 and for LDL-C <3.5 mmol/L, statin is indicated if Apo B ≥1.2 g/L or Non-HDL-C ≥4.3 mmol/L or men >=50 and women >=60 if they were smokers, had impaired fasting glucose, or hypertension, and low HDL). [1]
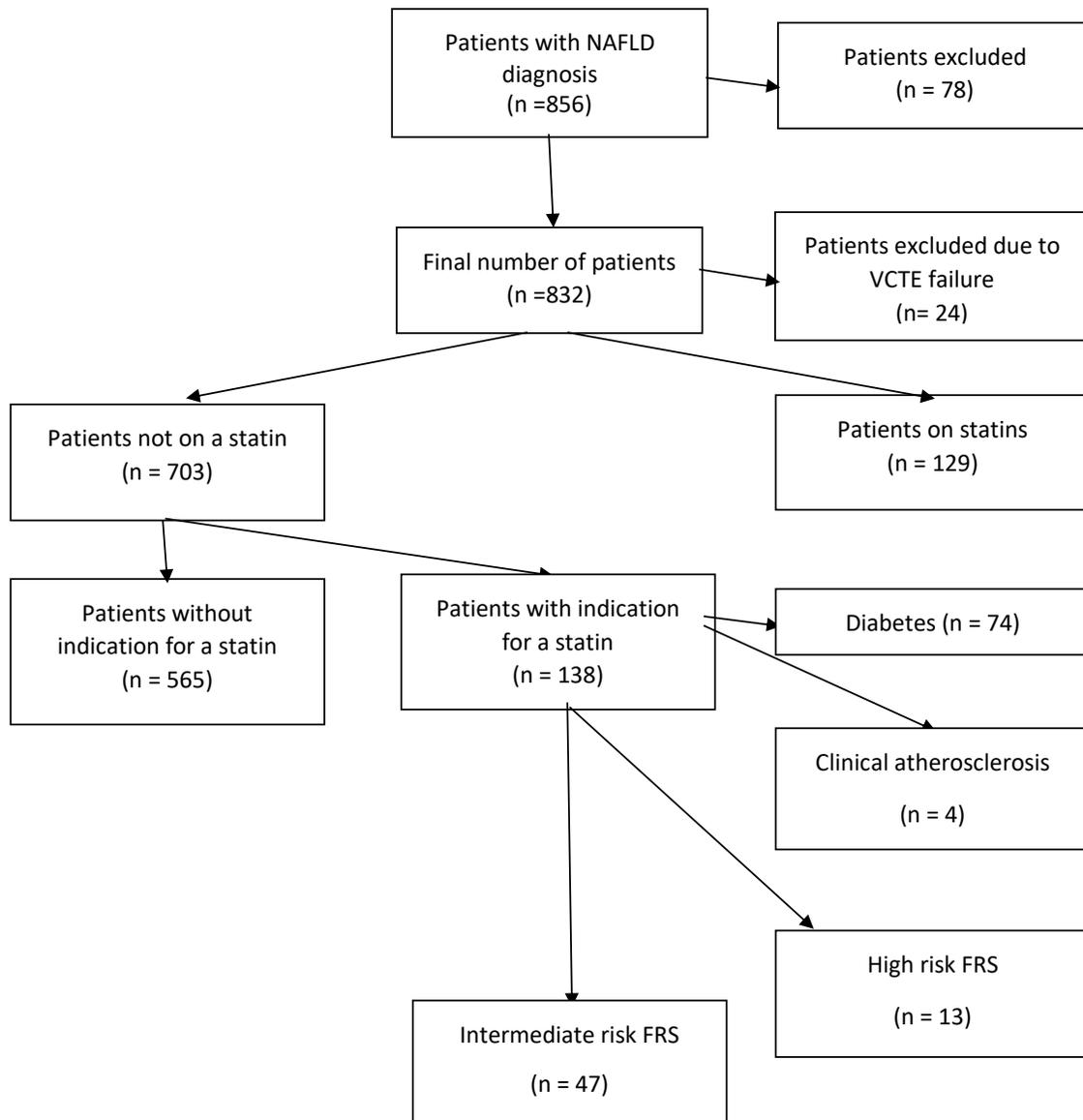
For our operational definition of "indication for a statin", all patients that were already on a statin were considered to have indication for a statin.

In 319 patients FRS could not be directly calculated due to missing values of systolic blood pressure. In these cases, we conducted a multiple imputation procedure with the aregimpute command from the Hmisc package (FE Harrell).[2,3] Variables in the imputation model were age, BMI, total cholesterol, and diabetic status. We created 10 initial complete datasets with imputed systolic blood pressure where we determined the FRS (A). Since office blood pressure measurements were not conducted with in many occasions according to guideline

recommendations, and recent data shows that blood pressure measurements in trials are lower (by ~5 mmHg) than same patient's out of trial office measurements,[4] we created 10 additional datasets by decreasing systolic blood pressure by 5 mmHg (B) and 10 additional datasets decreasing systolic blood pressure by 10 mmHg (C).

The median percentage of patients with indications for a statin and not on a statin was 53.26% in (A) datasets, 51.14% in (B) datasets and 49.41% in (C) datasets, suggesting that the impact of blood pressure variability or our imputation procedure in the classification of patients as with or without indication for a statin was negligible.

For all further analysis and operational classification according to indication for a statin, we selected at random one of the (B) datasets. The figure shows the final numbers of patients with indications for a statin according to our algorithm.

Supplemental material

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┌─────────────────────┐          ┌─────────────────────┐
│  Patients with NAFLD│─────────▶│  Patients excluded  │
│      diagnosis      │          │      (n = 78)       │
│     (n =856)        │          │                     │
└─────────────────────┘          └─────────────────────┘
         │
         ▼
┌─────────────────────┐          ┌─────────────────────┐
│ Final number of     │─────────▶│ Patients excluded   │
│     patients        │          │ due to VCTE failure │
│     (n =832)        │          │      (n= 24)        │
└─────────────────────┘          └─────────────────────┘
      ╱        ╲
     ╱          ╲
    ▼            ▼
┌──────────────────┐   ┌─────────────────────┐
│ Patients not on  │   │ Patients on statins │
│    a statin      │   │      (n = 129)      │
│    (n = 703)     │   └─────────────────────┘
└──────────────────┘
    │      ╲
    ▼       ╲
┌────────────────┐  ┌──────────────────┐   ┌─────────────────────┐
│ Patients       │  │ Patients with    │──▶│  Diabetes (n = 74)  │
│ without        │  │ indication for   │   └─────────────────────┘
│ indication for │  │ a statin         │   ┌─────────────────────┐
│ a statin       │  │  (n = 138)       │──▶│ Clinical            │
│ (n = 565)      │  └──────────────────┘   │ atherosclerosis     │
└────────────────┘      │       ╲          │      (n = 4)        │
                        │        ╲         └─────────────────────┘
                        ▼         ╲        ┌─────────────────────┐
            ┌────────────────┐     ╲──────▶│  High risk FRS      │
            │ Intermediate   │             │      (n = 13)       │
            │ risk FRS       │             └─────────────────────┘
            │  (n = 47)      │
            └────────────────┘
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References:

1. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Canadian journal of cardiology*. 2016;32(11):1263-1282. https://search.datacite.org/works/10.1016/j.cjca.2016.07.510. doi: 10.1016/j.cjca.2016.07.510.

2. Fienberg SE. Springer series in statistics. *Springer Series in Statistics*.

3. Frank E Harrell Jr, with contributions from Charles Dupont and many others. (2020). Hmisc: Harrell Miscellaneous. R package version 4.4-0. https://CRAN.R-project.org/package=Hmisc

4. Drawz PE, Agarwal A, Dwyer JP, et al. Concordance between blood pressure in the systolic blood pressure intervention trial and in routine clinical practice. *JAMA internal medicine*. 2020. http://dx.doi.org/10.1001/jamainternmed.2020.5028. doi: 10.1001/jamainternmed.2020.5028.