Common illnesses including high cholesterol prompt hunt for personalized drugs

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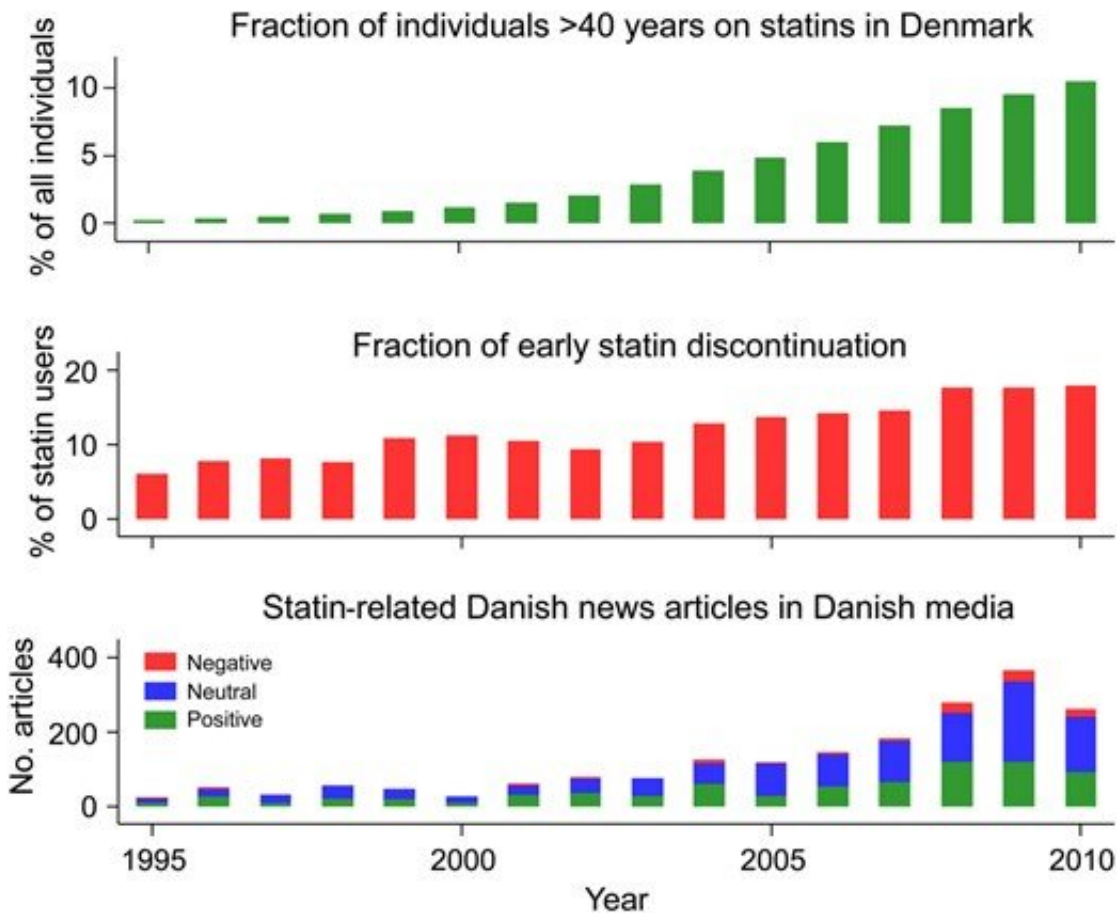

The percentage of individuals in the entire Danish population aged 40 or older on statins (top panel), the percentage discontinuing statin use within 6 months following start of statin therapy (middle panel), and the number of negative, neutral, and positive statin-related news stories published during 1995–2010 in Denmark. We studied all individuals on statins during 1995–2010 in the entire Danish population, comprising 583 349 (86%) who continued statin use and 91 551 (14%) who discontinued early. Credit: *European Heart Journal* (2015). DOI:

10.1093/eurheartj/ehv641

Better tailoring prescriptions to the unique biological make-up of each patient could lead to big improvements in health.

One size does not necessarily fit all. This is as true in medicine as in most other areas of life. People can react very differently to the same treatment and the results are potentially very serious.

Consequently, it can be difficult for doctors to decide on exactly which drug to prescribe to patients with the same presenting symptoms but very different genetic and biological make-ups. Research in the field of personalized medicine is seeking to tailor drug prescriptions to individual profiles more effectively.

Cholesterol case

At the University of Helsinki in Finland, the IndiviStat project is looking at the use of statins as a case in point. This common cholesterol-reducing medication is one of the most widely prescribed drugs in Europe—and indeed the world. Statins are credited with reducing the threat of illness and death in people at risk of heart disease by lowering their 'bad' cholesterol levels.

Unfortunately, a common side effect is muscle pain, which can cause some people to stop taking these drugs. The consequences can be fatal. A 2015 Danish study, published in *European Heart Journal*, found that forgoing prescribed statins increased the risk of heart attack by 26%.

"There may be 20 000 to 30 000 excess deaths worldwide because people stop taking this therapy," said Professor Mikko Niemi, a

University of Helsinki clinical pharmacologist who is leading the project.

Niemi has been researching how gene mutations affect people's reactions to statins since the early 2000s.

The ERC grant of €2 million that he received in 2017 will help him design an algorithm to aid doctors in choosing the most suitable statin—there are about half a dozen to pick from—for each patient. At the push of a button, the algorithm will use the results of a genetic test to evaluate how the patient's body is likely to react and select the one best adapted to the person.

"Differences with statins are not in what the drug does to the body, but in how the body handles the drug," said Niemi.

Muscle test

All statins work the same way—by blocking the manufacture of low-density (bad) cholesterol in liver cells. But in some people, their liver can be predisposed to take up less of the drug so that more of it circulates in their blood.

As levels of statin in the blood go up, the risk of muscle toxicity rises. This can lead to the muscle pain that causes some people to stop taking the drugs.

Towards the end of the research project, the algorithm will be tried out on between 500 and 1 000 Finnish patients who are to be prescribed the cholesterol-lowering drugs.

"We hope we can reduce the number of patients who stop taking statins from around 30% to 20%," Niemi said.

Such a result could save thousands of lives.

All right

Statins are not the only life-altering medicines that could benefit from new approaches better tailored to individuals.

Personalized medicine is a medical model that aims to tailor the right therapeutic strategy for the right person at the right time.

It can help determine a patient's predisposition to disease and propose the correct treatment, based on the individual's unique situation, before an illness has progressed too far. The European Commission has been supporting research in personalized medicine for many years.

Professor Sara Marsal at the Vall d'Hebron Research Institute in Barcelona, Spain is studying six inflammatory diseases within the context of the DocTIS project. It involves research organizations from Italy, Germany, Spain, Sweden, the UK and the US.

The diseases being looked at include psoriasis, Crohn's and rheumatoid arthritis. On the face of it, these seem quite different, impacting skin, bowel and joints. Yet doctors have long recognized that their symptoms overlapped.

As a young doctor, Marsal recalls how patients seeing a dermatologist for psoriasis would be sent to her for arthritis, for example.

"These diseases are highly prevalent chronic conditions and we have no cures," she said.

Then, 20 years ago, the link was confirmed in a positive way when a group of drugs—TNF inhibitors—targeting inflammation were found to

reduce symptoms in patients with all three disorders. More recent studies revealed shared genetics between the conditions.

Patients with these inflammatory conditions also have common experiences.

Their disease may flare up, improve for periods but never go away. They can be prescribed a drug, which reduces symptoms, but over time these benefits fade. A doctor then prescribes a different treatment. The patient may or may not respond to the drug.

Biobank help

Marsal has a plan to do better through DocTIS, which runs for six years through 2025. The other three diseases being assessed are ulcerative colitis, lupus and psoriatic arthritis.

The project is tapping a biobank, which Marsal helped to build, that stores thousands of biological samples from patients with chronic inflammatory diseases.

Researchers will look at patient cells, proteins and genes at the start of a treatment. This is to help understand the biology associated with a treatment response.

The individual will have either responded or not responded after three months of therapy. The project intends to identify, at a molecular and cellular level, the reasons for differences in response and better target existing treatment.

"We urgently need to understand the biology behind responders and non-responders in order to predict what the result will be of using some of these drugs together," said Marsal.

Drug duos

Experiments in cells, and then in animals, will pinpoint likely drug duos for patients with any one of the six inflammatory diseases. Towards the end of the project, a clinical trial will administer these combinations to patients. If successful, it will help clinicians match specific patients with existing drugs.

"We are striving for higher efficacy, without safety concerns," said Marsal. "This would be a fantastic outcome."

Usually, developing a new drug could take a decade—with no guarantee of success. However, this new approach with existing drugs means that patients might benefit from a new combination at the end of the project, in around three to four years.

Before then, Marsal and her colleagues hope to publish results that will help scientists and doctors better understand the biological foundations that lie beneath these chronic inflammatory diseases.

In Helsinki, Niemi's ambition is for his statin-choosing algorithm to be available not just in Finland or in Europe but worldwide. With heart and inflammatory diseases being such common ailments, both projects have the potential to improve the health of countless people.

More information: Sune Fallgaard Nielsen et al, Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study, *European Heart Journal* (2015). DOI: 10.1093/eurheartj/ehv641

IndiviStat: cordis.europa.eu/project/id/725249

DocTIS: cordis.europa.eu/project/id/848028