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# Statins for primary prevention in patients ages 75 years and more: lack of evidence and shared decision

## INTRODUCTION

Statins have demonstrated dose-dependent efficacy in lowering LDL-cholesterol (LDL-c) levels[1]. That said, the level of evidence concerning their clinical efficacy varies according to type of prevention. After a major cardiovascular event, five randomized placebo-controlled trials have demonstrated the beneficial effects of statins on all-cause mortality and occurrence of a new event. As regards prevention of an initial cardiovascular event, a 2013 *Cochrane* review included 19 placebo-controlled trials and more than 56,000 participants. Overall mortality and risk of cardiovascular event were reduced in statin-treated patients. These results were questionable given the fact that when taking the mortality criteria alone into consideration, only in one study was the result significant[3].

In 2014 the scientific council (CS, in French) of the national college of teachers in general practice (CNGE) put forward a recommendation on strategies to be adopted in primary prevention for persons less than 75 years of age[4]:

- To initiate or pursue statin treatment for patients at high cardiovascular risk; statin at high or moderate doses according to overall level of cardiovascular risk, patient comorbidities and tolerance;
- To give up therapeutic strategies targeted at LDL-c levels, as well as repeated LDL-c control, which has not been validated in randomized controlled trials.

In 2017, the scientific council expressed its disagreement on the points in the updated recommendations of the French health authority (HAS) on dyslipidemia management strategies that remain based on LDL-c thresholds and targets[5,6].

As regards patients aged 75 years or more, a review of (a) the literature on large-scale randomized placebo-controlled trials of statins and (b) meta-analyses including patients treated with statins in so-called "primary" prevention found not a single randomized trial having specifically included patients in the above age bracket[7]. While the PROSPER[8], JUPITER[3] and CARDS[9] studies and a 2013 meta-analysis[10] all included some subjects more than 75 years of age, analysis of these subgroups did not demonstrate the interest (or lack of interest) of statin prescription as primary prevention in this population.

According to the recommendations of the French agency for health product sanitary safety (AFSSAPS), which was superseded in 2012 by the French national agency for drug and health product safety (ANSM), the possibilities of

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extrapolating existing results to elderly persons were limited[11].

The 2013 recommendations by the American College of Cardiology called for prudence with regard to persons over 75 years old, emphasizing that prior to prescription of a statin, consideration of the benefit/risk balance should be commonsensical[12]. As for the US Preventive Services Task Force (USPTF), it was unable in this specific context to come up with any recommendations[13]. Statins can bring about adverse effects, essentially myalgia, as well as drug interactions. Moreover, a low total cholesterol level is associated with increased mortality among patients over 75 years old[14].

The benefit/risk balance of statin-based primary prevention in terms of all-cause mortality and avoidance of cardiovascular events has yet to be determined in persons over 75 years old. It is consequently rather surprising to note that in 2012, nearly 600,000 individuals in that age bracket were being treated by statins in so-called primary prevention[7].

The objective of this study was to better understand, through exploration their relevant experience in medical practice, the factors determining statin prescription by general practitioners (GP) confronted with this situation. The term "prescription" could refer to either the decision to prescribe, or the decision not to prescribe.

## METHOD

Using a comprehensive paradigm, our approach was qualitative. Data collection was carried out through semi-structured interviews with GPs, of which the contents were subjected to thematic analysis[15]. Interview guidelines were drawn up by two researchers, and were tested during two initial interviews that took place in April 2016, after which the "probing" questions were modified (**sidebar**).

**1. What do you think about statins for patients more than 75 years old in primary prevention?**

Probing questions: Are you aware of any recommendations? Of topic trees?

**2. Can you tell us about your most recent statin prescription in primary prevention for a patient over 75 years of age?**

Probing questions: On the basis of which medical criteria do you decide in this context to introduce a statin?
What are the other criteria taken into ac count when making a decision?
If there is no prescription: What are the reasons?

**3. By the same token, can you tell us about the most recent situation in which you discontinued statin prescription in primary prevention for a patient over 75 years of age?**

Probing questions: On the basis of which medical criteria did you decide in this context to discontinue the statin prescription?
Can you envision other criteria being taken into account when making a decision?
What are the difficulties that you may have encountered in this context?

**4. As regards the question on statins in primary prevention for a patient over 75 years of age, what are the observations that you might wish to add?**

**Sidebar -** Interview guidelines

GP recruitment came about through targeted, volunteer, purposive sampling in which sex and age as well as site and type of practice were taken into account. Varied experience within the sample was actively sought out. The GPs were contacted (a) directly in their offices by a researcher; (b) by e-mail when a professional circle was involved; or (c) by telephone using the directory. The interviews took place in the physicians' offices from April through June 2016; they were conducted by a single researcher who had been preliminarily trained to apply qualitative research interview techniques. Following the oral agreement of each participating GP, the discussions were recorded. Anonymous processing procedures were explained, as was the possibility of "opting out" of the interview at any time without being required to justify having done so; if necessary, the recording could be erased or deleted.

Interview recruitment proceeded until data saturation had been achieved. It continued on an ongoing basis, from April to September 2016 in parallel with the interviews.

The contents of the interviews were transcribed by a researcher in a Word® file in the form of verbatim reports; non-verbal data (silences, attitudes...) were noted in the margins. The verbatim reports regarding each physician's responses, listed as P1 through P13, constituted the corpus of the study. The data were rendered anonymous.

Analysis of the verbatim re-

ports was thematic and inductive. A disaggregated list of themes involving a certain level of organization was drawn up, and each of the themes was compared and classified according to significant inferences in a theme-based journal. During this phase, some themes were grouped together in salient thematic clusters corresponding to a heading under which it was possible to include several themes related to the study objectives. Synthesis and structuring of the attendant data using Xmind Pro 3.5.2® software led to construction of a schematic topic tree. At each step of the analysis, triangulation by the two researchers was carried out. And finally, while the article was being written, the Consolidated criteria for reporting qualitative research (COREQ) were scrupulously observed[16].

No opinion or ethical authorization was requested for this study, which was built around interviews with GPs, involved no intervention, and took place before the Jardé law on research involving human beings was enacted (in November 2016).

## RESULTS

All in all, 34 GPs were contacted. While 4 refused to participate, 10 did not reply and 7 were not recontacted because data saturation had been achieved as of the 10th interview. The characteristics of the physicians interrogated are detailed in the **Table**.

The main result is that in the absence of recommendations, physicians made their decisions to prescribe or not to prescribe according to individual situations, and the patients' viewpoints were taken into account.

Four main thematic focuses appeared:

### Scientific data were not discriminatory decision-making criteria

The recommendations were either not well-known or described as unsuitable, occasionally extrapolating data from studies of younger patients. The participating physicians were at times perplexed, asking themselves whether the problems arose from gaps in their knowledge or gaps in the medical literature, in which case there clearly existed a need for more complete information prior to prescription: "*It is true that if there were more of a consensus on the subject, it might be easier; maybe there is and I've forgotten it*" (P02).

Cardiovascular risk factors were mentioned in relation to decision-making but were in some instances confused with the notion of cardiovascular events in secondary prevention. LDL-c level was not cited as a discriminatory criteria. Some of the physicians did not take it into account at all, whereas others took it into consideration when it was exceedingly high.

Data on the risks of adverse effects and fear of drug interactions were widely known and mentioned as elements contributing to their decisions to prescribe or discontinue prescription of a statin: "*They are summarily discontinued because of*

| Physician | Sex | Age (years) | Activity duration (years) | Medical practice site | Interview duration |
|---|---|---|---|---|---|
| P01 | Female | 52 | 20 | Semi-rural, group | 8 min |
| P02 | Female | 28 | 0* | Two group practices | 13 min 46 |
| P03 | Male | 40 | 10 | Rural | 9 min 49 |
| P04 | Female | 29 | 0-5 | Semi-rural, group | 8 min 11 |
| P05 | Female | 40 | 5 | Semi-rural, group | 5 min 46 |
| P06 | Female | 45 | 10 | Semi-rural, group | 6 min 44 |
| P07 | Female | 55 | 23 | Rural in a care home | 6 min 02 |
| P08 | Male | 50 | 15 | Urban, group | 10 min 51 |
| P09 | Male | 55 | 27 | Urban, group | 10 min 55 |
| P10 | Male | 65 | 36 | Urban | 9 min 28 |
| P11 | Male | 58 | 28 | Urban | 6 min 05 |
| P12 | Male | 44 | 5 | Urban, group | 7 min 23 |
| P13 | Male | 59 | 29 | Semi-rural | 5 min 10 |

Table - Characteristics of the physicians interrogated
* :*SASPAS resident*.

*myalgia, asthenia, even at 75 a lowering of sex drive can occur...And so, in those cases, me, I stop prescribing*" (P01); "*Finally it's the fear of being more deleterious than effective, you know*" (P07).

**The physicians' experiences were heterogeneous**

While some of the GPs were convinced of the usefulness of statins among the elderly, others were opposed to their prescription and/or called their usefulness into question.

Practice and experience were the key decision-making factors. The predictable non-compliance of some patients and previous experience of adverse effects disposed some physicians to refrain from prescribing. They mentioned how hard it was not only to discontinue, but also to start statin treatment: "*It's difficult to initiate and it's difficult to put an end to it, indeed*" (P03).

Duration of medical practice could also influence prescription-related decisions. While younger GPs spoke in general terms about how hard it was to suspend previously existing treatments, their more experienced colleagues evoked seemingly ingrained prescription habits. When treatment was discontinued, some participating physicians felt the need to remotely monitor cholesterol rate: "*Often enough I cancel [the prescription] and monitor at three months*" (P06).

On another score, the notion of "physiological age" appeared to render artificial the utilization of "75 years old" as a negative milestone or barrier. The physician were inclined to perceive a given patient in his or her totality: "*At 75 years of age, there are persons who remain highly active, very dynamic, with high life expectancy, and it is our wish to protect them...*" (P07).

**Prescription takes into account the patient and his relationship with the physician**

The GPs placed patient-associated determining factors at the heart of the decision-making process. Patients' "beliefs", which ranged from hostility toward statins to fear of excess cholesterol, could render discussion problematic. Their use of alternative treatments (herbal medicine, red yeast rice) was taken into account notwithstanding (a) absent proof of efficacy; and (b) adverse effects similar to those reported in the literature on statins. Patients' opinions and choices were part and parcel of negotiations and shared decision-making. The quality of the physician-patient relationship was experienced as essential to the course of treatment: "*We are not treating cholesterol level, we are caring for a patient" (P03); "The patient's choice … of course … all the time*" (P01).

**The media and the environment influence the decision-making process**

When deciding on prescription, the GPs were frequently subjected to external influences. Messages expressing hostility toward statins were purveyed by the media and led to numerous requests for treatment discontinuation. Recent declarations and polemics concerning statins contributed to a climate hardly propitious to reasoned discussion. That said and in spite of everything, the GPs were convinced that the influence of an attending physician was more pronounced than that of the media. "*I do not see people who say to me: 'Oh! I saw that program... We must stop right now!' No, they are rather trusting, so I find*" (P07).

Hospitalization in geriatrics or medicine generally entailed treatment cessation. Conversely, cardiologists were prone to pressure the GPs and their patients by fanning fear of the effects of discontinuation. The patient's friends and family and the notion of polypharmacy likewise had to be taken into consideration, and the physicians insisted on the importance of moral, medical-legal and ethical responsibility when making a decision to prescribe or stop prescribing a statin. "*I did not willingly initiate statin treatment* [laughter], *even though I am the one who wrote out the prescription and am finally as responsible, if not more responsible for this prescriptionthan the cardiologist* " (P02).

## DISCUSSION

This study is the first to explore, in a context of uncertainty, the factors determining prescription of statins for elderly persons in primary prevention. A qualitative approach was conducive to the emergence of original data. The GPs engaged in pragmatic reasoning, which was influenced by the context in which prescriptions were given (or not). Their overall approach to decision-making was closely interwoven with the basic concepts of evidence-based medicine (EBM) through which different dimensions are taken into account[17,18]. And in this type of situation, given the weakness of existing scientific proof, other decision-determining factors come into play. It is by no means astonishing that in circumstances calling for a holistic problem-solving approach, our inductively constructed topic tree wound up bearing a resemblance to the different circles characterizing EBM.

The singularity of the study consisted in the fact that none of the participating physicians explicitly spelled out a mode of reasoning stemming from this model; everything proceeded "as if" application of EBM were tacit and implicit. The factors determining decision-making brought into play (a) a peculiar situation; (b) the physician's experience; (c) the patient's standpoint and; (d) the influence of the overall environment. The doctors indubitably assigned primordial importance to the physician-patient relationship.

The "three circles" of evidence-based clinical decisions are currently considered as the paradigm for research in the medical sciences premised on evidence-based medicine. Just like any other one, the paradigm undergoes evolution, and numerous articles have recently recommended that it be rethought or (re)considered in all of its dimensions[19]. So it was that in 2003, the aforementioned three circles were redefined as "research evidence", "patient's preferences and actions", "clinical state and circumstances (patient/physician)"; the last circle supersedes "clinical experience", and more precisely specifies the clinical circumstances perhaps proper to a particular doctor and a particular patient; the general environment and societal evolutions are being taken increasingly into account. Shared medical decision-making, which is essential to the results of our study entails discussion that would fundamentally characterize the physician-patient relationship. It deserves the support allowing the different possible options, including non-action, to be envisioned according to the available evidence; in this context, patient preferences could be openly expressed[20].

The CNGE has undertaken a project called "Rebuilding the evidence base", of which to the objective is "to evaluate the clinical efficacy and also the risks of drugs, using a structured, reproducible and transparent method"[21]. The authors underline the fact that EBM is closely associated with shared medical decision-making and that information must be presented to the patient in suitable, understandable terms.

In the present study, lack of informative evidence enabling enlightened choice complicated the shared decision-making process. However, the GPs adapted by taking patient preferences into account whenever the relational framework allowed. Their degree of adaptation amidst scientific uncertainty attests to the salience of the EBM model and underscores its implicit use by GPs. In this context, taking patient preferences into account and keeping open the option of non-drug intervention represent strategies meriting further development. Prescription-related reasoning could consequently be constructed in close complementarity with the patient.

The GPs participating in our study insisted on the medical-legal or ethical aspect of their decision to prescribe (or not). The decision-making competence considered as central to EBM entails the "virtuous handling of uncertainty" inculcated by the World Organization of National Colleges (WONCA) and the Academies and Academic Associations of General Practitioners (AAGP) and is central to the notion of quaternary prevention[22]. With regard to persons more than 75 years old, whose life expectancy is limited, prescription of statins or other drugs, particularly supposedly preventive treatments some of which produce side effects, is never anodyne.

Controversy about statins and a tendency to confuse cardiovascular risk factors with previous cardiovascular events influenced the prescription habits of the physicians participating in our study. Secondary prevention indications have been followed by harmful discontinuations triggered by polemics having to do with … primary prevention. In 2016, the international review of reference *Lancet* published argumentation aimed at rehabilitating statins from the standpoint not only of physicians, but also of the general public[23]. The main conclusion was that age-independently, the benefit/risk balance of statins in secondary prevention remains markedly positive.

The physicians participating in our study voiced concern over the lack of relevant scientific data and insisted on their need for recommendations enabling them to better prescribe. An ongoing Australian study including patients over 70 years of age, *Statin Therapy for Reducing Events in the Elderly*[24], is aimed at assessing the efficacy of statins in primary prevention. As for the French SAGA study (*Statine Au Grand Age*), its objective is to evaluate, in primary care, the clinical and medical-economic interest of discontinuing statin prescription for persons more than 75 years old being treated in primary prevention[25].

As regards our study method, existing criteria of scientific validity in a qualitative study were observed, and those of the aforementioned COREQ grid were applied as we write this article. Verisimilitude was furthered by the choice of participants: present-day general practitioners with experience in prescription. Had other criteria

been privileged, the results might have been different; for example, we could have postulated "training program supervisor" as a sought-after profile; in point of fact, we did not apply an *a priori* hypothesis in an exploratory perspective.

Internal validity was ensured by researcher triangulation. The doctors interviewed did not reread the verbatim reports (or the analysis) and could consequently not fully ensure external validity. Resistance was verified by data saturation. Coherence was obtained by projecting as objectives: (a) exploration of the physicians' representations; (b) use of suitable interview guidelines; and (c) apposite choice of analysis methodology. Oude Engberink[19] has demonstrated that qualitative health care research represents an opportunity to rethink EBM by exploiting its capacity to explore, and even to probe into the experience of physicians and patients in their actual, real-life contexts. With this in mind, the highlighting of prescriber profiles in a context of uncertainty would have been relevant, but our verbatim reports did not allow them to emerge. On this subject, Bloy has drawn up a cartography of medical uncertainty and detailed the various ways in which it is handled by GPs26. Had we explored this field, we would have better understood how physicians go about decision-making in a context of uncertainty, particularly as regards statin prescription. The position of the researcher carrying out the interviews (a young doctor, still in training) may have influenced verbatim collection by inhibiting the emergence of factual statements (fear of being judged, perhaps on the basis of type of prescription). It would have been interesting to analyze this type of influence by allowing the physicians to comment on the interviews. The two physician-researchers were compelled to place their personal representations of the study topic "on the back burner".

## CONCLUSION

This original qualitative study facilitated comprehension of the factors determining statin prescription for elderly persons in primary prevention and primary care in a context of scientific uncertainty. The concepts pertaining to evidence -based medicine enabled us to successfully incorporate the latter. Improved prescription necessitates shared decision-making involving the patient and taking into account his or her particular circumstances. Studies leading to Grade A recommendations will be needed so as to eliminate (or reduce) the uncertainties on statins in this context. More generally, questions have been raised and will continue to be raised about drug prescription for elderly persons in primary prevention.

**Summary**

Context. A review of the scientific literature does not lead to conclusive results on the usage of statins in primary prevention for subjects that are over 75 years old. A 2015 review of literature did not find any randomized clinical trial that specifically targeted people over 75 years old.

Objective. The study's objective was to understand general practitioners' motives when prescribing statins for the elderly given this lack of scientific evidence.

Method. A qualitative study with semi-structured interviews was conducted with a group of general practitioners. Analysis of thematic content until reaching data saturation, and data triangulation of the analysis by two researchers. Results. The decision to prescribe statins in primary prevention for elderly patients was essentially based on motives related to general practitioners as well as patients' choices: a shared decision with the patient, individual evaluation, and the physician's experience. Scientific motives were under-represented, even though in some cases, cardiovascular risk factors and ldl-cholesterol levels could influence decisions. General practitioners were sensitive to the risk of side effects, drug interactions, and to quality of life of elderly people.

Conclusion. General practitioners are not unconscious of the context of a scientific gap. Using the evidence based medicine (ebm) model would improve their decision-making process. However, the question of the ethics of such a prescription is to be considered. A randomized clinical trial is necessary as well as the medico-economic study saga (statines au grand age) to help to define the place of statins in primary prevention for people over 75 years old.

➜ Keywords: statine, primary prevention, elderly, qualitative research.

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