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# Compliance of oral isotretinoin use with prescription and delivery guidelines between 2014 and 2021 in France [1212]

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## Abstract

### Introduction

Due to adverse effects of isotretinoin, prescription and dispensation guidelines recommended to use it as a second-line treatment, to renew the prescription for each dispensation and to perform laboratory monitoring. In June 2015, a decision of regulatory authorities restricted treatment initiation to dermatology specialist.

To evaluate the compliance of oral isotretinoin use to national guidelines between 2014 and 2021 in France.

### Methods

A retrospective cohort study was conducted using data from the National Health Data System and included all new users of oral isotretinoin between 2014 and 2021. Initiation corresponded to the first dispensation of isotretinoin with no prior dispensation for at least 12 months. Four outcomes were assessed: the initial prescription by dermatology specialist, the second-line prescription after systemic antibiotic and/or topical therapy, the renewal of prescription for each dispensation, and carrying out lipid and hepatic enzymes laboratory monitoring. The effect of the decision of June 2015 on the direct (step) and prolonged (trend) changes in proportion of treatment initiated by dermatology specialist was assessed using a monthly interrupted time series analysis (ARIMA model). We expressed the results of this model as change in proportion (%), 95% confidence intervals (95%CI) and p-value (p).

### Results

We included 552,221 patients (mean age: 24 years; sex ratio: 0.95). The percentage of treatment initiated by a specialist increased from 88% to 92% after June 2015. Time series analysis showed a significant immediate increase (2.93%, 95%CI 1.71% to 4.15%,  $p < 0.01$ ) but no significant change in trend over time (0.08%, 95%CI -0.23% to 0.09%,  $p = 0.39$ ). Within 12 months before initiation, 63% of patients received at least one dispensation of systemic antibiotic therapy and 42% received at least one dispensation of systemic antibiotic and topical therapy. In average, 86% of dispensations had a new prescription. 80% of patients had lipid and hepatic enzymes monitoring before treatment initiation and 41% during treatment.

### Conclusion

Guidelines on initial prescriber and renewal of prescription were mostly respected while compliance to guidelines on second-line prescriptions and biological monitoring was inadequate.

## Background & Objectives

Despite the demonstrated effectiveness of isotretinoin on acne, it is associated with adverse effects such as teratogenic risks, psychiatric effects and metabolic disorders (1). Previous pharmacovigilance studies revealed inadequate compliance with guidelines, and new measures have been implemented (2,3):

- May, 2015** French National Agency for the Safety of Medicines and Health Products (ANSM) measure restricting first-time prescriptions to specialists in dermatology
- December, 2018** Update of risk reduction measures documents (RRMs) for patients and healthcare professionals and a new information campaign targeting healthcare professionals
- January, 2019** by the ANSM

## Objectives

To evaluate the effect of the ANSM measures on the initiation of treatment with oral isotretinoin and compliance with the Summary of Product Characteristics (SmPC) between 2014 and 2021:

- Renewal of the prescription at each dispensation
- Second-line prescription of isotretinoin after first-line treatment with oral systemic antibiotics and topical treatments
- Restriction of the first-time prescription to specialists in dermatology
- Realization of lipid and hepatic enzymes laboratory monitoring

## Results

N= 552 221



Mean age: 24,3 years ( $\pm$  11y)  
67% patients aged 11 to 24 years



51% of women



9% of patients with complementary solidarity health

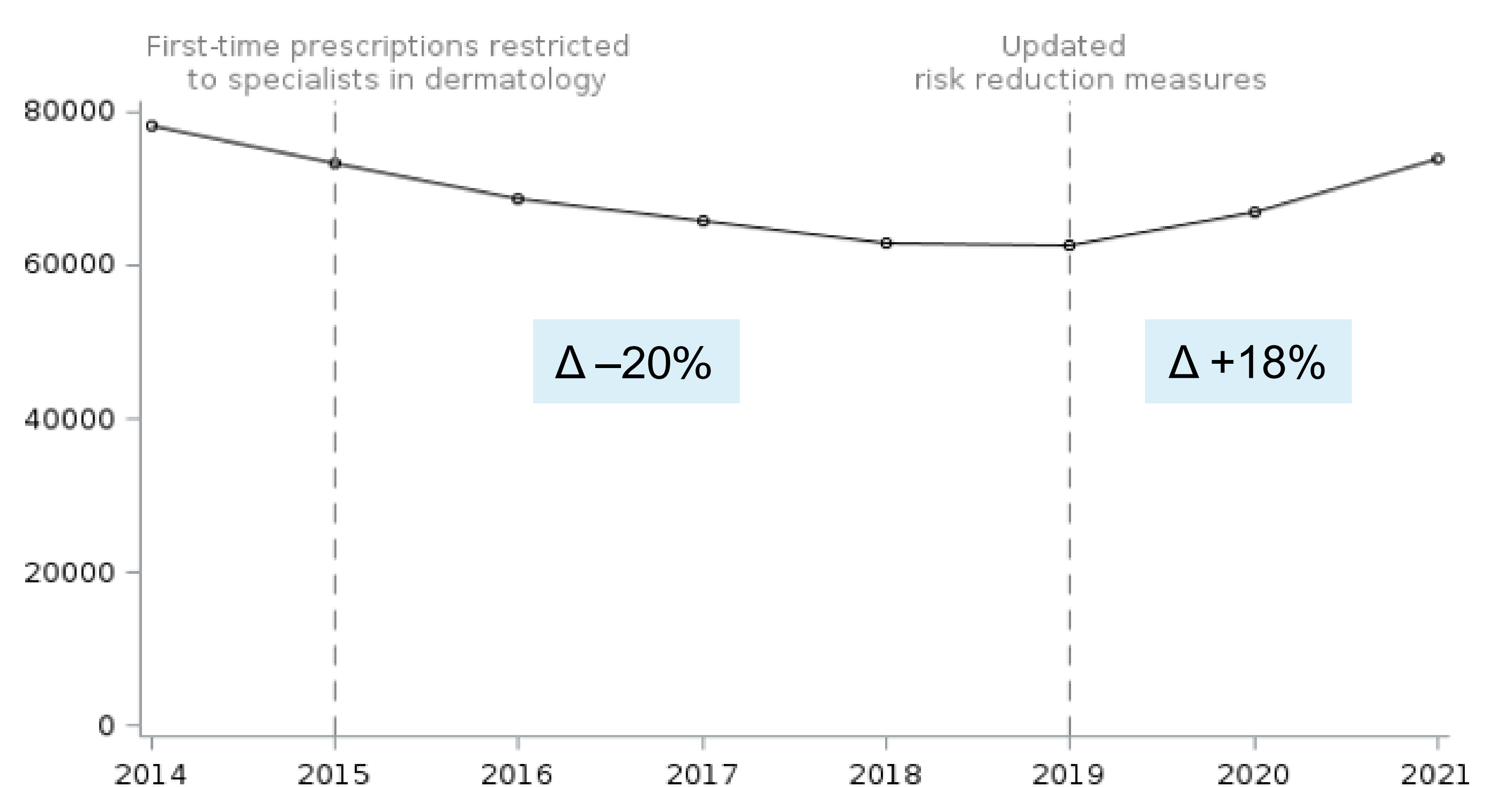


Mean duration of treatment : 191 days ( $\pm$  112d)



86% of dispensations made with a new prescription

Number of initiations of treatment with oral isotretinoin over the period 2014-2021



Time series analysis

Measure	Step	Ramp	p-value
May, 2015	- 205.00 [- 950.26 ; 540.27]	- 29.57 [- 54.93 ; - 4.21]	$p=0.590$
January, 2019	322.93 [- 533.53 ; 1179.39]	50.92 [ 8.02 ; 93.81]	$p=0.460$

## Second-line prescription of isotretinoin

63% of treatments with at least one prior dispensation of a systemic antibiotic in the year preceding the initiation

19% of treatments initiated after a well-conducted systemic antibiotic therapy

13% of treatments preceded by a well-conducted systemic antibiotic therapy and with at least one dispensation of a topical treatment

Well-conducted systemic antibiotherapy = at least 3 dispensations of a systemic antibiotic within a 180-day window the year preceding the initiation of isotretinoin

Systemic antibiotics indicated for the treatment of acne = Doxycycline, Limecyclyne, Minocycline or Erythromycin

Topical treatments indicated for the treatment of acne = Erythromycin, Clindamycin, Benzoyl peroxide or Retinoid

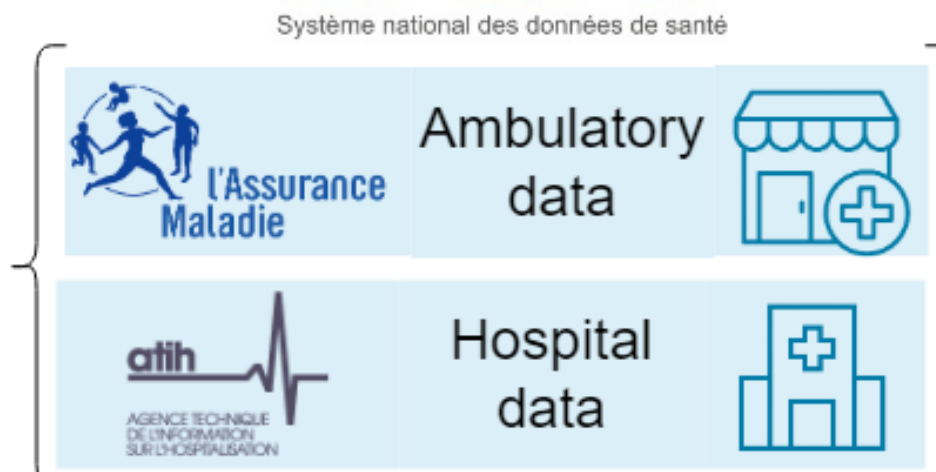
## Conclusions

- Decrease in initiations, associated with the 2015 measure, and increase between 2019-2021
- Compliance regarding the renewal of prescriptions almost reached 90%
- Upward trend in the number of treatments initiated by a dermatology specialist

## Data & Methods

### Data source

SNDS  
Système national des données de santé

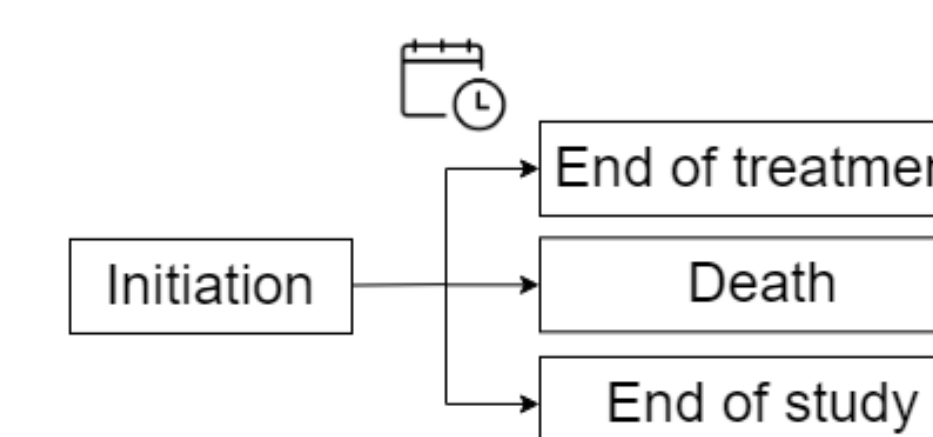


### Study design

Population-based retrospective cohort study

- Patients who initiated treatment with oral isotretinoin between 2014 and 2021
- Having a previous dispensation of oral isotretinoin during the 12 months preceding inclusion

### Follow-up



## Descriptive analyzes

- Isotretinoin treatment initiations and evolution between 2014 and 2021
- Socio-demographic and medical characteristics of patients at initiation
- Characteristics of treatments and prescribers
- Realization of biological monitoring

## Time series analyzes (Seasonal ARIMA models)

- Number of treatment initiations
- Proportion of treatments initiated by a specialist in dermatology (2015 measure only)

## Restriction of the first-time prescription to specialists in dermatology



91% of initiations by specialists in dermatology

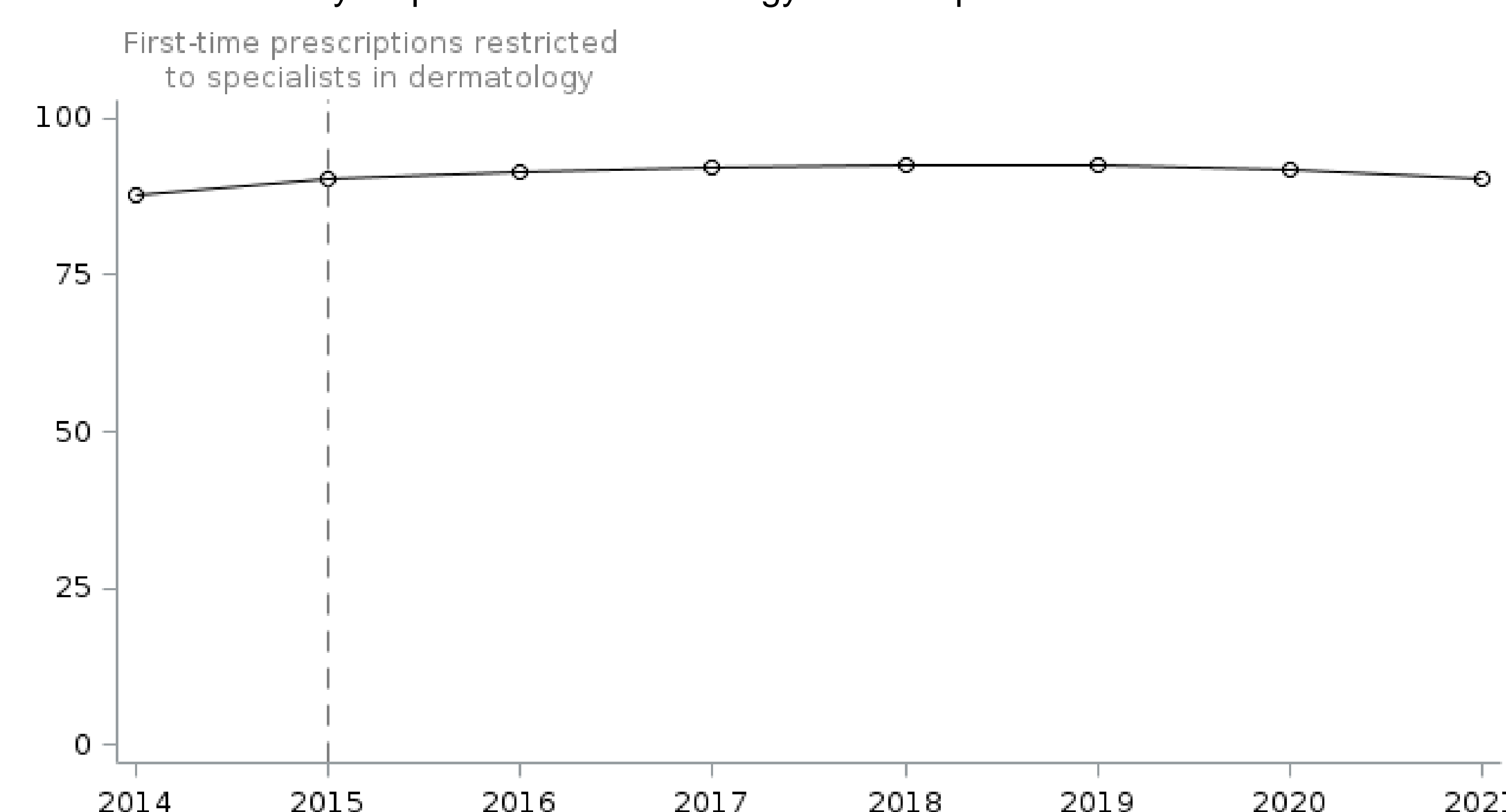
94% of prescriptions in those treatments are renewed by specialists in dermatology



6% of initiations by general practitioners

70% of prescriptions in those treatments are renewed by general practitioners

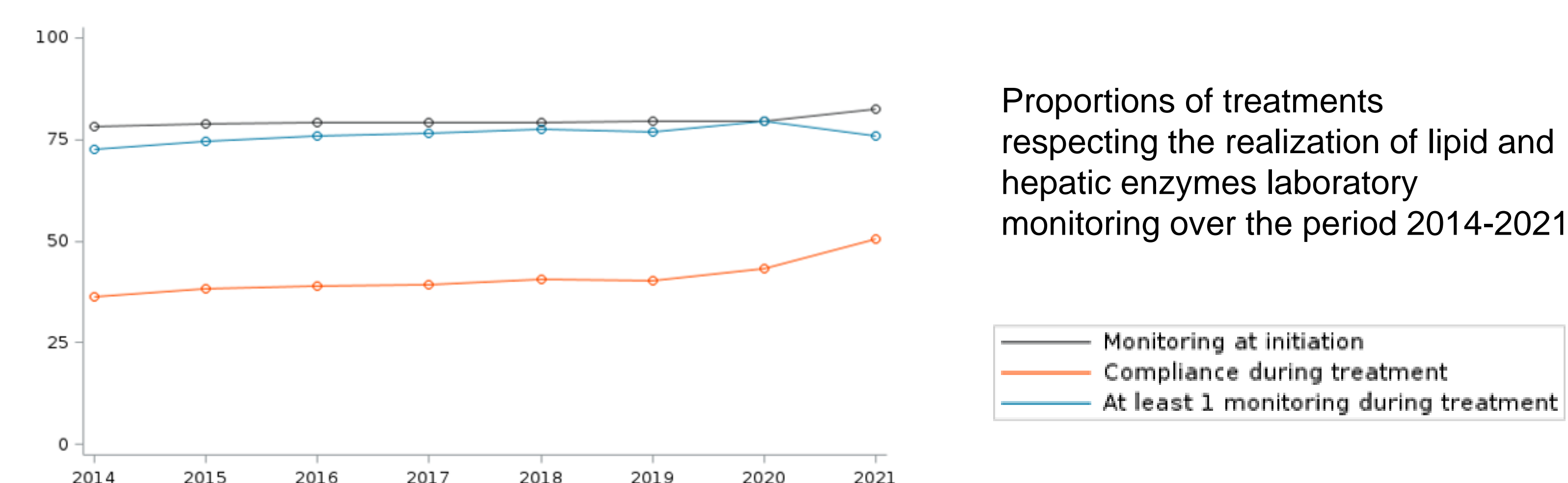
Proportions of treatments with a primo-prescription made by a specialist in dermatology over the period 2014-2021



Time series analysis

Measure	Step	Ramp	p-value
May, 2015	2.93% [1.71 ; 4.15]	- 0.07% [- 0.23 ; 0.08]	$p<0.001$

## Realization of lipid and hepatic enzymes laboratory monitoring



Proportions of treatments respecting the realization of lipid and hepatic enzymes laboratory monitoring over the period 2014-2021

Monitoring at initiation  
Compliance during treatment  
At least 1 monitoring during treatment

- 2/3 of treatments preceded by antibiotherapy and only 1/10 of treatments preceded by well-conducted first-line treatment
- Compliance with biological monitoring well followed at the initiation but less during the treatment



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The authors declare absence of conflicts of interest