# Are targeted treatment recommendations in chronic hepatitis C tailored to diagnostic methods of fibrosis?

Sylvie Deuffic-Burban[1,2] PhD ( sylvie.burban@inserm.fr), Jérôme Boursier[3,4] MD (JeBoursier@chu-angers.fr), Vincent Leroy[5,6] MD (VLeroy@chu-grenoble.fr), Yazdan Yazdanpanah[2,7] MD (yazdan.yazdanpanah@bch.aphp.fr), Laurent Castera[8,9] MD (laurent.castera@bjn.aphp.fr), Philippe Mathurin[1,10] MD (philippe.mathurin@chru-lille.fr)

[1] Inserm, LIRIC-UMR995, F-59000 Lille, France; Univ Lille, F-59000 Lille, France

[2] Inserm, IAME, UMR 1137, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France

[3] CHU d'Angers Service d'Hépato-Gastroentérologie, Angers, France

[4] HIFIH, UPRES 3859, SFR 4208, Univ LUNAM, Angers, France

[5] CHU de Grenoble Clinique Universitaire d'Hépato-gastroentérologie, Pôle Digidune, Grenoble, France

[6] Inserm U823, IAPC Institut Albert Bonniot, Grenoble, France

[7] AP-HP, Hôpital Bichat, Service de maladies Infectieuses et tropicales, F-75018 Paris, France

[8] AP-HP, Hôpital Beaujon, Service d'Hépatologie, Clichy, France

[9] Inserm U773, Univ Paris Diderot, Sorbonne Paris Cité, Clichy, France

[10] CHRU Lille, Hôpital Huriez, Service des Maladies de l'Appareil Digestif et de la Nutrition, Lille, France

Corresponding author

Sylvie Deuffic-Burban, Inserm LIRIC-UMR995, 8 rue Jean Walter, 59000 Lille, France, Tel: 33 3 20 44 59 62 (extension 35128), sylvie.burban@inserm.fr

Keywords

Cirrhosis; liver complications; liver deaths; Interferon-free therapy; Markov model; Noninvasive markers of fibrosis; targeted therapy; therapeutic strategy; universal therapy

Word count: 6598

Number of Figures and tables: 3 Figures, 3 Tables

List of Abbreviations

HCV, hepatitis C virus

CHC, chronic hepatitis C

IFN-free, interferon-free

SVR, sustained virologic response

Conflict of interest statement: Sylvie Deuffic-Burban reports grants from Janssen, Merck; personal fees from Abbvie, BMS, Gilead, HEVA, Janssen, Merck, Public Health expertise. Jérôme Boursier reports personal fees from Janssen, Gilead, Synageva. Vincent Leroy reports personal fees from Janssen, Abbvie, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, Roche. Yazdan Yazdanpanah reports personal fees from Abbott, Bristol-Myers Squibb, Gilead, MSD, Roche, Tibotec, ViiV Healthcare. Laurent Castera reports grants from Janssen; personal fees from Abbvie, Biopredictive, Bristol-Myers Squibb, Echosens, Gilead, Janssen, Merck. Philippe Mathurin reports grants from Janssen; personal fees from Janssen, MSD, Bristol-Myers Squibb, Gilead, Norgine.

Financial support statement: This study received an unrestricted grant from Janssen Pharmaceuticals. This grant has paid the costs of meetings and conference calls between co-authors to validate the model results. The funder was not involved in designing the study, interpreting the data, preparing the article, or deciding to submit it for publication.

Authors contributions: All authors have made substantial contributions to the intellectual content of the paper. Sylvie Deuffic-Burban and Philippe Mathurin have had the conception and design of the work. Jérôme Boursier, Vincent Leroy, Laurent Castera and Yazdan Yazdanpanah acquired and analyzed the data. Sylvie Deuffic-Burban performed the modelling. All authors contributed to interpretation of data. Sylvie Deuffic-Burban and Philippe Mathurin drafted the work. All authors revised it critically for important intellectual content and approved the final version to be published. Philippe Mathurin obtained funding. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere.

**ABSTRACT (250 words)**

**Background and aims**: This study quantifies the impact of different rules for access to treatment, ranging from targeted therapy in patients with ≥F3 in Italy, ≥ severe F2 in France, and universal therapy in UK, using noninvasive diagnostic tests of fibrosis to determine targeted therapy. **Methods**: A country-specific Markov model predicts outcomes with targeted and universal interferon-free therapy vs. no treatment in the three countries. Targeted therapy was initiated in patients ≥F2 (F2-scenario) or ≥F3 (F3-scenario) evaluated by noninvasive diagnostic tests according to the real stage of fibrosis. Base-case analysis considered targeted therapy only once (using the baseline evaluation of fibrosis). Assuming that each assessment was independent from the previous one, an alternative analysis considered yearly assessment of fibrosis to target additional treatment in newly identified patients with significant fibrosis. **Results**: Universal therapy is the most effective strategy and reduced the 5-year incidence of cirrhosis by 12.0-17.7, liver complications by 4.2-5.3 and liver deaths by 3.7-4.7, vs. no treatment. In base-case analysis, the F2-scenario using FibroScan or patented blood biomarkers reduces the 5-year incidence of cirrhosis by 2.7-4.0, liver complications by 3.5-3.7 and liver deaths by 3.3-3.7, vs. no treatment. The results of the F3-scenario are poor for the incidence of cirrhosis, and moderately effective for the liver complications. The alternative analysis with a yearly assessment of fibrosis improves the impact of targeted therapy. **Conclusion**: By quantifying the impact of different scenarios of targeted therapy and universal therapy, this study could help health agencies and experts to draft therapeutic guidelines.

**LAY SUMMARY**

The impact of different treatment strategies was evaluated in three countries, France, Italy and UK, using a mathematical model. This analysis showed that:

- A prioritization strategy of HCV treatment for patients with advanced disease would decrease the overall impact of treatment on morbidity and mortality

- A strategy initiating HCV treatment to all would already show a benefit in reducing 5-year morbidity and mortality.

## INTRODUCTION

The progression of chronic hepatitis C virus (HCV) infection varies significantly depending on patient characteristics. Around 20% of patients develop cirrhosis, while others never develop extensive fibrosis over 20 years of infection [1, 2]. We have shown that the patterns of the natural history of chronic hepatitis C (CHC) were significantly different in 6 European countries and that the impact of antiviral therapy in reducing the incidence of cirrhosis and deaths varies in these countries [3]. The extent of fibrosis, a marker of disease progression, is assessed by noninvasive tests or liver biopsy [4-6]. Available noninvasive tests include a physical technique based on measurement of liver stiffness using transient elastography [7] and a biological approach based on serum biomarkers of fibrosis [8-11].

Viral eradication following antiviral therapy resolves the risk of developing cirrhosis and reduces the risk of complications in patients with cirrhosis. Effective therapeutic strategies could include treating all patients whatever the severity of fibrosis or, as recommended by current guidelines, targeting those at risk of death from liver disease [4, 5]. For the targeted strategy, experts from EASL and AASLD recommend administering antiviral therapy to patients with fibrosis stage ≥ F2 and giving the highest priority to those with advanced fibrosis (Metavir F3-F4) [4, 5]. **It** is also acknowledged that priorities may be modulated according to local and/or societal considerations [5]. Indeed, reimbursement of oral regimens combining anti-NS5b with anti-NS5a and/or anti-NS3 differs in different countries, with universal treatment except in patients with genotype 3 HCV in UK [12-14], treatment of fibrosis stages severe F2 to F4 in France [15], and only stages F3-F4 in Italy [16, 17]. The targeted strategy **is often presented as** the best option for health systems in a context of prioritization of resources, even in high income countries. **This strategy aims to initiate treatment in patients who are most in need related to their risk of complications of liver disease, without taking into consideration the broader impact of hepatitis C on people's lives.** It is based on the assumption that antiviral therapy will be offered to untreated patients as soon as their disease progresses. However, this strategy is

associated with a risk of misclassifying patients because of the limits of the diagnostic tests of fibrosis. When treatment is initiated in patients with fibrosis stage ≥ F2, certain patients with fibrosis F0-F1 will be candidates for treatment ("false positives"), and some patients with fibrosis F2-F4 will not ("false negatives"). In addition, data are still lacking for the value of noninvasive tests in detecting the progression of fibrosis in patients without or with mild/moderate fibrosis at baseline [18].

The goal of the present study was to evaluate the consequences of targeted and universal therapy for HCV-related morbi-mortality based on the use of noninvasive diagnostic tests in three countries; France, Italy and UK. In response to a context of prioritization of resourcing for health systems, we chose a 5-year period for application of targeted therapy instead of a long-term analysis.

## METHODS

### Study design

We used a country-specific decision model to predict clinical outcomes in patients with chronic HCV mono-infection over 5 years. We evaluated interferon-free (IFN-free) direct-acting antiviral regimens according to the following therapeutic strategies: no treatment, targeted therapy based on the stage of fibrosis (F2 or F3), and treatment regardless of stage of fibrosis stage (universal treatment). For targeted therapy, treatment was initiated in patients with ≥ F2 (F2-scenario) or ≥ F3 (F3-scenario) based on the diagnosis obtained by noninvasive tests. Targeted therapy was also evaluated using two hypothetical diagnostic tests of fibrosis: a perfect test for the diagnosis of fibrosis that would provide the patient's real stage of fibrosis determined by the model; a useless test with no accuracy to diagnose fibrosis that would result in treating 50% of the population whatever the real stage of fibrosis.

In the base-case analysis, targeted therapy was determined only once using the baseline evaluation of fibrosis, meaning that patients would not be offered treatment at all during the 5-year period when being diagnosed in stage <F2 for F2-scenario and in stage < F3 for F3-scenario. In an alternative analysis, fibrosis was evaluated each year assuming that each assessment was independent from the previous one resulting in the initiation of treatment in newly identified patients with significant fibrosis.

### Model structure

The natural history of chronic HCV infection was based on a country-specific Markov model described in the supplementary material (Supplementary **Fig. S1**. and Supplementary Tables S1-S2) [3, 19]. The study population was stratified for each country-specific model according to patient characteristics (Supplementary material and Supplementary Table S3). Treatment with IFN-free

regimens leading to sustained virologic response (SVR) rates >85%-90% was introduced into the natural course of the disease for each therapeutic strategy until age 70 (Supplementary Table S4).

**Input parameters**

*Study population (Supplementary material and Table S3)*

In 2014 patients with CHC, F0-4, between 18-70 years old (who were aware or not of their infection) were estimated using a previously published back calculation model [3] that was updated for France [20]: 131,000 in France, 666,000 in Italy and 209,000 in the UK. For the present study, only patients who were aware of their infection and thus candidates for therapy were simulated: 56,250 in France, 268,500 in Italy and 57,100 in the UK.

We distributed each population according to treatment history based on previous modeling studies [3, 20], i.e. treatment-naïve (49% in France, 84% in Italy and 82% in UK) vs. treatment-experienced. We also estimated the distribution of fibrosis and the main risk factors of the progression of fibrosis (i.e. age, gender and alcohol abuse) in 2014 [3, 20]. Finally, we took into account the differences in genotype distribution in these three countries: 62% of patients with genotype 1, 8% with genotype 2, 17% with genotype 3 and 13% with genotype 4 in France [20]; 59%, 12%, 23% and 6% respectively in Italy [3]; and 44%, 17%, 35%, 4% respectively in the UK [3].

The distribution of fibrosis estimated in 2014 was considered to be the real stage of fibrosis that was used to estimate the evaluated stage of fibrosis by noninvasive methods.

*Data of the evaluation of fibrosis (Table 1)*

The evaluated stage of fibrosis was estimated according to the diagnostic accuracy of the different methods: liver stiffness measurement by FibroScan®, patented blood biomarkers of fibrosis (FibroTest®, Hepascore®, Fibrometer®), FIB4 and APRI, two unpatented serum biomarkers of

fibrosis. We calculated the probability (or weighted means of probability for patented blood marker tests FibroTest®, Hepascore® and Fibrometer®) of being classified by each method as stage ≥ F2 or ≥ F3 for each stage of fibrosis using individual data from previously published studies [21]. The thresholds of fibrosis ≥ F2 and ≥ F3 for each noninvasive score were based on prior publications [7, 9, 11, 22-24]: 7.0 and 9.5 for FibroScan, 0.49 and 0.59 for FibroTest®, 0.5 (no available threshold for fibrosis ≥ F3) for Hepascore® and 0.411 and 0.628 for Fibrometer®, respectively. We used the different validated cut-offs for FIB4: 0.6 (FIB4-0.6 = all patients with FIB4 ≥ 0.6 were classified as fibrosis ≥ F2) and 1.0 (FIB4-1.0 = all patients with FIB4 ≥ 1.0 were classified as fibrosis ≥ F2) for fibrosis ≥ F2; 1.45 (FIB4-1.45 = all patients with FIB4 ≥ 1.45 were classified as fibrosis ≥ F3) and 3.25 (FIB4-3.25 = all patients with FIB4 ≥ 3.25 were classified as fibrosis ≥ F3) for fibrosis ≥ F3 [25]. We also used the two validated cut-offs for fibrosis ≥ F2 (no available threshold for fibrosis ≥ F3) for APRI [11]: 0.5 (APRI-0.5 = all patients with APRI ≥ 0.5 were classified as fibrosis ≥ F2) and 1.5 (APRI-1.5 = all patients with APRI ≥ 1.5 were classified as fibrosis ≥ F2).

For example, a patient whose real stage of fibrosis is F2 will have 1/2 chances to be classified as ≥ F2 by FibroScan (53%) and 1/10 chances by APRI-1.5 (11%) (Table 1a).

**Clinical outcomes**

The cumulated incidences of cirrhosis, of liver complications of cirrhosis (hepatocellular carcinoma and/or decompensated cirrhosis) and of liver deaths were assessed over 5 years in the absence of treatment, with targeted therapy according to therapeutic strategies (F2- and F3-scenario) with base-case or alternative analysis, and with universal therapy (regardless of the stage of fibrosis). The incidence of cirrhosis was calculated in patients with fibrosis stage F0-3 while the incidence of complications and those of liver-related deaths were calculated in patients with fibrosis stage F0-4.

**Sensitivity analysis**

Sensitivity analyses were conducted to evaluate the impact of uncertainties on our overall conclusions. Specifically, we assessed the impact of uncertainties around fibrosis progression rates and around estimates for each diagnostic method of fibrosis. For each sensitivity analysis, we evaluated 5-year outcomes based on boundaries intervals provided in Supplementary Table S1 and Table 1.

## RESULTS

### Base-case analysis: targeted therapy according to one assessment of fibrosis (at baseline) versus universal treatment

*Cumulated incidence of cirrhosis over 5 years*

**Fig. 1A.** and Table 2 present the cumulated incidence of cirrhosis over 5 years in France according to different therapeutic strategies: no treatment, targeted therapy according to the F2-scenario, targeted therapy according to the F3-scenario, and universal treatment. In the absence of treatment, the incidence of cirrhosis increases from 2.5% to 12.4%. As expected, universal therapy results in the lowest incidence of cirrhosis: between 0.1% and 0.7% (corresponding to a 17.7-reduction for 5-year incidence of cirrhosis). Targeted therapy with an IFN-free regimen decreases the incidence of cirrhosis in both scenarios compared to no treatment: for example, using patented blood biomarkers, the 5-year incidence of cirrhosis decreases by 2.3 (F3-scenario) to 3.3 (F2-scenario). However, APRI-1.5 and FIB4-3.25 are not effective as shown by the higher incidence of cirrhosis than that with a useless test (i.e. a test which has a 0.5 AUROC). The F3-scenario is always less effective than the F2-scenario: for example, the 5-year cumulated incidence of cirrhosis using patented blood biomarkers is 5.3% with the F3-scenario and 3.8% with the F2-scenario. Third, the use of noninvasive tests with targeted therapy always results in higher incidence of cirrhosis than the hypothetical perfect test (i.e. perfect staging of fibrosis), except with the use of FIB4-0.6 due to the lack of specificity leading to treat the most of patients (Table 1). Indeed, in the F2-scenario, the 5-year incidence of cirrhosis with noninvasive diagnostic tests is 2.5 (patented blood biomarkers) to 6.8-times higher (APRI-1.5) than with the perfect test.

In Italy and the UK, universal and targeted therapy based on different diagnostic methods of fibrosis reduces the cumulated incidence of cirrhosis compared to no treatment (**Fig. 2A.**, **Fig. 3A.** and

Supplementary Tables S5-S6). APRI-1.5 is ineffective **because of higher incidence of cirrhosis than that with a useless test**, and F3-scenario is also less efficient than F2-scenario in those countries.

Absolute numbers of cirrhosis are different in the three countries (Tables 2, S5-S6): without treatment, around 6,000 new cases of cirrhosis would occur over 5 years in France, 22,600 in Italy and 650 in the UK; and with F2-scenario and patented blood biomarkers, around 1,800 new cases of cirrhosis would occur over 5 years in France, 7,100 in Italy and 200 in the UK.

*Cumulated incidence of liver complications over 5 years*

In France (**Fig. 1B**. and Table 2), the cumulated incidence of liver complications increases from 1.6% to 8.2% in the absence of treatment. Universal treatment once again results in the lowest incidences: from 0.3% to 1.6% (corresponding to a 5.1-reduction in the 5-year incidence of liver complications). The incidence of liver complications with targeted therapy with an IFN-free regimen decreases compared to that with no treatment. For example, the 5-year incidence of cirrhosis decreases by 2.8 (F3-scenario) to 3.6 (F2-scenario) using FibroScan. Again, APRI-1.5 and FIB4-3.25 are not effective compared to other tests. The F3-scenario is still less efficient than the F2-scenario. For example, the 5-year cumulated incidence of liver complications using FibroScan is 2.9% with the F3-scenario vs. 2.3% according for the F2-scenario.

The cumulated incidence of liver complications in Italy and the UK with universal and targeted therapy was reduced compared to no treatment (**Fig. 2B.**, **Fig. 3B.** and Supplementary Tables S5-S6). The absolute numbers of liver complications are different among the three countries (Tables 2, S5-S6). Without treatment, around 4,600 liver complications would occur in France over 5 years, 17,300 in Italy and 1200 in the UK. For example, with the F2-scenario and FibroScan, around 1,300 liver complications would occur over 5 years in France, 4,900 in Italy and 320 in the UK.

*Cumulated incidence of liver-related deaths over 5 years*

In France (**Fig. 1C**. and Table 2), in the absence of treatment, the incidence of liver-related deaths increases from 0.1% to 4.3%. Universal treatment results in the lowest incidence, between 0.1% to 1.0%. Targeted therapy with noninvasive tests decreases the incidence of liver-related deaths while the results with F2 and F3 scenarios are similar. APRI-1.5 and FIB4-3.25 are still ineffective.

The cumulated incidence of liver-related deaths decreases in Italy and the UK with universal and targeted therapy compared to no treatment (see **Fig. 2C.**, **Fig. 3C.** and Supplementary Tables S5-S6). As for other outcomes, the absolute numbers of liver-related deaths differ among the three countries (Tables 2, S5-S6). Without treatment, around 2,400 liver deaths would occur over 5 years in France, 8,800 in Italy and 610 in the UK. For example, with the F2-scenario and FibroScan, around 700 liver deaths would occur over 5 years in France, 2,600 in Italy and 170 in UK.

**Alternative analysis: targeted therapy according to yearly assessment of fibrosis versus universal treatment**

**Fig. 1D.**, **Fig. 1E.**, **Fig. 1F.** and Table 3 present the cumulated incidences of cirrhosis, liver complications and deaths over 5 years in France according to the different therapeutic strategies: no treatment, targeted therapy according to the F2-scenario with yearly assessment of fibrosis, targeted therapy according to the F3-scenario with yearly assessment of fibrosis, and universal treatment. Targeted therapy based on yearly assessment of fibrosis had more impact for all clinical outcomes than that based on one baseline assessment of fibrosis. Even with repeated assessment, APRI-1.5 and FIB4-3.25 are still ineffective as shown by higher incidences of clinical outcomes compared to those with a useless test. The F2-scenario is more effective than the F3-scenario for the cumulated incidence of cirrhosis: for example, the 5-year cumulated incidence of cirrhosis using patented blood biomarkers

is 2.0% with the F3-scenario vs. 1.3% with the F2-scenario. However, the results of the F3-scenario and the F2-scenario are similar for liver complications.

Similar trends were obtained in Italy (**Fig. 2D.**, **Fig. 2E.**, **Fig. 2F.** and Supplementary Table S7) and UK (**Fig. 3D.**, **Fig. 3E.**, **Fig. 3F.** and Supplementary Table S8).

**Sensitivity analysis**

Uncertainties around fibrosis progression rates on cumulated incidence of cirrhosis, liver complications and liver-related deaths at 5 years are presented in Supplementary Tables S9-S10 for France, Supplementary Tables S11-S12 for Italy, and Supplementary Tables S13-S14 for UK. The results varied very slightly, except for UK because of greater uncertainties around progression rates. Uncertainties around estimates for each diagnostic method of fibrosis are provided in Supplementary Tables S15-S16 for France, Supplementary Tables S17-S18 for Italy, and Supplementary Tables S19-S20 for UK. The main results remained unchanged.

**DISCUSSION**

The present study shows that targeted therapy based on the use of FibroScan or patented blood biomarkers would decrease the 5-year cumulated incidence of HCV-related clinical outcomes. Concerning FIB4, in F2-scenario, the two cut-offs (0.6 and 1.0) led treating a high proportion of F0-F1 patients. In F3-scenario, the use of 3.25 cut-off cannot be recommended, whereas the use of 1.45 cut-off is as efficient as the patented blood biomarkers. The value of APRI was not confirmed, in particular with the 1.5 cut-off. Moreover, this method cannot be applied for F3-scenario. The F3-scenario is not effective for the incidence of cirrhosis and liver complications compared to the F2-scenario. Universal therapy is the strategy with the best clinical outcomes. A theoretical scenario of yearly assessment of fibrosis improves the results of targeted therapy, based on the assumptions that each evaluation was independent from the previous one.

FibroScan and patented blood biomarkers are relevant for use with targeted therapy because they identify the subset of patients with an increased risk of developing cirrhosis, liver complications and death. These results illustrate the outcome of targeted therapy based on their use. This approach should be considered in relation to the different rules for access to treatment with reimbursement for universal treatment in the UK (except genotype 3), targeted therapy in patients with ≥ severe stage F2 in France, and ≥ F3 in Italy. These different rules have been decided by expert consensus groups and health agencies who have based their recommendations in part, on the number of patients to be treated, the high cost of treatment and available resources.

Limiting access to therapy, with prioritization to patients with advanced disease, is one strategy to address the question of cost. However, **first this strategy of prioritization would decrease the overall impact of treatment on morbi-mortality. As highlighted in our study, universal treatment would already show a benefit in reducing 5-year morbidity and mortality. This benefit would be amplified considering a long-term period. Second, this strategy of prioritization** generates some difficulties as it will delay progress towards HCV elimination [26].

WHO is likely to introduce HCV elimination targets, which include a 65% reduction in HCV-related deaths and a 80% reduction in HCV incidence by the year 2030 [27]. Achieving the WHO mortality and incidence elimination targets is estimated to be cost-effective in Australia where >80% of all prevalent HCV infections are attributable to injecting drug use [28]. In other settings, universal therapy has been shown to be cost-effective [29, 30]. **However, the establishment of universal treatment justifies a discussion between governments and pharmaceutical industries aiming to reduce drug costs. The French Government had negotiated a steep discount from Gilead Sciences for Sovaldi, setting the retail price of the drug at the lowest in Europe. Germany obtained the same price several months later. France also negotiated for further discounts if volume hits certain targets, as well as for rebates for any patients on which the treatment didn't work. But, even at these prices, treating all people with CHC, without costs related to increasing screening and diagnosis rates, would have a major budget impact [29]. Costs should probably continue to decrease. Despite high prices,** some high-income countries (e.g. Germany, Scotland and Australia) have announced decisions to provide treatment for all persons infected with HCV. This was also recently **considered** by the French Ministry of Health for the next coming months. However, in a context of HCV elimination targets, wide-scale HCV screening is another main issue that in addition would lead to the highest impact in terms of morbi-mortality [3].

Although there were small differences in terms of liver deaths between the F2- and F3- scenarios, our study shows the poor results of the F3-scenario for the incidence of cirrhosis - the hidden part of the iceberg - and liver complications. However, the results of the F2-scenario are not as good as universal treatment for the incidence of cirrhosis and liver complications, especially based on one assessment of fibrosis. These drawbacks of targeted therapy cannot be overcome because they depend upon the misclassification of the noninvasive diagnostic methods of fibrosis. The value of our model is that the clinical consequences can be quantified providing a rational framework for public health decision-makers.

The results of this study show that reliable methods are needed to evaluate the progression of fibrosis over time [31]. Until now, the increase in scores over time reflecting disease progression has only been observed in patients with baseline scores that are already elevated [32]. This does not provide additional information to clinicians because patients with elevated noninvasive scores would have been treated after the first assessment. On the other hand, in patients with low scores at baseline, the progression of fibrosis to F2-F3 by repeated noninvasive testing has never been shown [33, 34]. In the absence of reliable data, we performed an alternative analysis assuming that each evaluation of fibrosis by a noninvasive method was independent from the previous one. This assumption is subject to question because a patient with fibrosis ≥ F2 who has been misclassified in a previous test may be correctly classified later, even if fibrosis has not progressed. Moreover, **yearly assessment of fibrosis would be difficult to set up in routine practice on broad population. Indeed,** such approach requires a highly organized process **with automatic recall system, better education of patients in terms of compliance and better quality of follow-up** that is not currently available in any of the three countries.

Our study has certain limitations. First, we did not perform an analysis combining FibroScan with patented blood biomarkers to increase their diagnosis accuracy. This approach would result in the treatment of a pool of 25% patients with discordant results between the two methods [7] and would probably results in results that are similar to our alternative analysis of the yearly assessment of fibrosis. Second, we did not evaluate the scenario in which clinicians initiated treatment in misclassified patients with obvious signs of disease progression such as low platelet count or splenomegaly. In such cases, the incidence of cirrhosis would not be modified because cirrhosis has already developed. Third, a liver biopsy was not considered due to the many procedures that would have been necessary and the high rate of contraindications and patient refusal that prevents its use for all CHC patients [18, 35]. Finally, we considered that 100% of the patients who were aware of their HCV status had a diagnosis of fibrosis that is an optimistic assumption. Also, noninvasive diagnostic

tests of fibrosis were assumed to be applicable in all cases. For example, we did not take into account the 11.7 to 15.8% risk of unreliable results for FibroScan [36, 37], and the cautions of use for serum markers in the presence of comorbidities (inflammatory process, alcohol consumption, rheumatoid arthritis, Gilbert syndrome, hemolysis, etc.) that affect some of the components of the score [18, 31]. Thus, the efficacy of the noninvasive diagnostic tests of fibrosis may have been overestimated, and the impact of targeted therapy as well.

In conclusion, the present study quantifies the impact of targeted therapy based on the use of noninvasive diagnostic tests of fibrosis. This could be useful for health agencies and experts to draft therapeutic guidelines.

**REFERENCES**

[1] Poynard T, Bedossa P, Opolon P, for the OBSVIRC, METAVIR, CLINIVIR, DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825-832.

[2] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418-431.

[3] Deuffic-Burban S, Deltenre P, Buti M, Stroffolini T, Parkes J, Muhlberger N, et al. Predicted effects of treatment for HCV infection vary among European countries. Gastroenterology 2012;143:974-985 e914.

[4] American Association for the Study of Liver Diseases (AASLD) & Infectious Diseases Society of America (IDSA). Recommendations for Testing, Managing, and Treating Hepatitis C. August 2014.

[5] European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015;63:199-236.

[6] European Association for the Study of the Liver. Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-264.

[7] Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.

[8] Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069-1075.

[9] Adams LA, Bulsara M, Rossi E, DeBoer B, Speers D, George J, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clinical chemistry 2005;51:1867-1873.

[10] Cales P, de Ledinghen V, Halfon P, Bacq Y, Leroy V, Boursier J, et al. Evaluating the accuracy and increasing the reliable diagnosis rate of blood tests for liver fibrosis in chronic hepatitis C. Liver Int 2008;28:1352-1362.

[11] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-526.

[12] National Institute for Health and Care Excellence. Sofosbuvir for treating chronic hepatitis C. NICE guidance 2015 [cited February 23, 2016]; Available from: https://www.nice.org.uk/guidance/ta330/resources/sofosbuvir-for-treating-chronic-hepatitisc-82602540657349

[13] National Institute for Health and Care Excellence. Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C. NICE guidance 2015 [cited February 23, 2016]; Available from: http://www.nice.org.uk/guidance/ta365/resources/ombitasvirparitaprevirritonavir-with-or-without-dasabuvir-for-treating-chronic-hepatitis-c-82602730453957

[14] National Institute for Health and Care Excellence. Ledipasvir–sofosbuvir for treating chronic hepatitis C. NICE guidance 2015 [cited February 23, 2016]; Available from: http://www.nice.org.uk/guidance/ta363/resources/ledipasvirsofosbuvir-for-treating-chronic-hepatitis-c-82602727094725

[15] ANSM. Liste des ATU de cohorte arrêtées. 2015 [cited May 27, 2015]; Available from: http://ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-de-cohorte-arretees/Liste-des-ATU-de-cohorte-arretees/

[16] Agenzia Italiana del Farmaco (AIFA). Sovaldi prescription criteria inItaly. 2015 [cited February 23, 2016]; Available from: www.agenziafarmaco.gov.it/sites/default/files/SOVALDI_Scheda_AIFA_10.12.2014.pdf

[17] Agenzia Italiana del Farmaco (AIFA). Aggiornamento epatite C. 2016 [cited February 23, 2016]; Available from: http://www.agenziafarmaco.gov.it/it/content/aggiornamento-epatite-c

[18] Castera L, Pinzani M. Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango? Gut 2010;59:861-866.

[19] Deuffic-Burban S, Schwarzinger M, Obach D, Mallet V, Pol S, Pageaux GP, et al. Should we await IFN-free regimens to treat HCV genotype 1 treatment-naive patients? A cost-effectiveness analysis (ANRS 95141). J Hepatol 2014;61:7-14.

[20] Deuffic-Burban S, Mathurin P, Pol S, Larsen C, Roudot-Thoraval F, Desenclos JC, et al. Impact of hepatitis C triple therapy availability upon the number of patients to be treated and associated costs in France: a model-based analysis. Gut 2012;61:290-296.

[21] Boursier J, de Ledinghen V, Zarski JP, Fouchard-Hubert I, Gallois Y, Oberti F, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology 2012;55:58-67.

[22] Poynard T, Imbert-Bismut F, Munteanu M, Messous D, Myers RP, Thabut D, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV FibroSure) and necrosis (ActiTest) in patients with chronic hepatitis C. Comparative hepatology 2004;3:8.

[23] Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013-1021.

[24] Boursier J, Bacq Y, Halfon P, Leroy V, de Ledinghen V, de Muret A, et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol 2009;21:28-38.

[25] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-1325.

[26] Zoulim F, Liang TJ, Gerbes AL, Aghemo A, Deuffic-Burban S, Dusheiko G, et al. Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. Gut 2015;64:1824-1833.

[27] World Health Organisation. Draft global health sector strategy on viral hepatitis, 2016–2021—the first of its kind. 2015 [cited July 20, 2016]; Available from: http://www.who.int/reproductivehealth/Hepatitis-global-strategy_Nov2015.pdf

[28] Scott N, McBryde ES, Thompson A, Doyle JS, Hellard ME. Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model. Gut 2016.

[29] Deuffic-Burban S, Obach D, Canva V, Pol S, Roudot-Thoraval F, Dhumeaux D, et al. Cost-effectiveness and budget impact of interferon-free direct-acting antiviral-based regimens for hepatitis C treatment: the French case. J Viral Hepat 2016;23:767-779.

[30] Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK, et al. Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. JAMA Intern Med 2016;176:65-73.

[31] Castera L, Pinzani M. Non-invasive assessment of liver fibrosis: are we ready? Lancet 2010;375:1419-1420.

[32] Vergniol J, Boursier J, Coutzac C, Bertrais S, Foucher J, Angel C, et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology 2014;60:65-76.

[33] Tamaki N, Kurosaki M, Tanaka K, Suzuki Y, Hoshioka Y, Kato T, et al. Noninvasive estimation of fibrosis progression overtime using the FIB-4 index in chronic hepatitis C. J Viral Hepat 2013;20:72-76.

[34] Cales P, Zarski JP, Chapplain JM, Bertrais S, Sturm N, Michelet C, et al. Fibrosis progression under maintenance interferon in hepatitis C is better detected by blood test than liver morphometry. J Viral Hepat 2012;19:e143-153.

[35] Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449-1457.

[36] Vergniol J, Foucher J, Terrebonne E, Bernard PH, le Bail B, Merrouche W, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140:1970-1979, 1979 e1971-1973.

[37] Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828-835.

Table 1 – Evaluation of the stage of fibrosis according to different tests: probability of patients being classified as fibrosis stage ≥ F2 (a) and ≥ F3 (b), in relation to the real stage of fibrosis [21, 35].

(a)

| Real stage of fibrosis | Probability of being classified as fibrosis stage ≥ F2 | | | | | |
|---|---|---|---|---|---|---|
| | FibroScan* | Patented blood biomarkers† | APRI-0.5‡ | APRI-1.5‡ | FIB4-0.6¥ | FIB4-1.0¥ |
| F0 | 35% [28-42%] | 9% [7-10%] | 4% [3-5%] | 0% [0-0%] | 66% [53-79%] | 23% [18-28%] |
| F1 | 26% [21-31%] | 29% [24-35%] | 29% [23-35%] | 2% [2-3%] | 82% [66-99%] | 48% [38-57%] |
| F2 | 53% [42-63%] | 63% [50-76%] | 57% [45-68%] | 11% [9-13%] | 94% [75-100%] | 74% [59-88%] |
| F3 | 80% [64-95%] | 83% [67-100%] | 72% [58-87%] | 24% [19-29%] | 98% [79-100%] | 91% [73-100%] |
| F4 | 98% [78-100%] | 97% [78-100%] | 93% [74-100%] | 45% [36-54%] | 99% [79-100%] | 94% [75-100%] |

*Threshold = 7.0 for FibroScan; †Weighted mean obtained with FibroTest (threshold = 0.49), Hepascore (threshold = 0.5) and FibroMeter (Threshold=0.411); ‡Two thresholds for APRI = 0.5 (APRI-0.5) and 1.5 (APRI-1.5); ¥Two thresholds for FIB4 = 0.6 (FIB4-0.6) and 1.0 (FIB4-1.0).

(b)

| Real stage of fibrosis | Probability of being classified as fibrosis stage ≥ F3 | | | |
|---|---|---|---|---|
| | FibroScan* | Patented blood biomarkers† | FIB4-1.45¥ | FIB4-3.25¥ |
| F0 | 6% [5-7%] | 2% [2-3%] | 12% [10-15%] | 0% [0-0%] |
| F1 | 11% [9-13%] | 17% [14-20%] | 23% [18-28%] | 2% [2-2%] |
| F2 | 20% [16-25%] | 45% [36-54%] | 49% [39-59%] | 6% [5-8%] |
| F3 | 58% [46-70%] | 72% [57-86%] | 73% [59-88%] | 20% [16-24%] |
| F4 | 96% [77-100%] | 94% [75-100%] | 88% [70-100%] | 41% [33-49%] |

*Threshold = 9.5 for FibroScan; †Weighted mean obtained with FibroTest (threshold = 0.59) and FibroMeter (Threshold=0.628); ¥Two thresholds for FIB4 = 1.45 (FIB4-1.45) and 3.25 (FIB4-3.25).

Table 2 – Cumulated incidence of clinical outcomes over 5 years (%) and at 5 years (N) in France according to different diagnostic methods of fibrosis and different therapeutic strategies with one assessment of fibrosis: no treatment, targeted therapy with F2-scenario, targeted therapy with F3-scenario, and universal treatment.

| | Time from first fibrosis evaluation (years) | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Cumulated incidence of cirrhosis | % | % | % | % | % | N* |
| No treatment | 2.5 | 5.0 | 7.5 | 10.0 | 12.4 | 6,000 |
| With useless test† | 1.3 | 2.7 | 4.0 | 5.3 | 6.5 | 3,200 |
| F2-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.6 | 1.0 | 1.5 | 730 |
| With FibroScan | 0.6 | 1.4 | 2.3 | 3.3 | 4.3 | 2,100 |
| With patented blood biomarkers | 0.5 | 1.2 | 2.0 | 2.8 | 3.8 | 1,800 |
| With APRI-0.5 | 0.8 | 1.7 | 2.7 | 3.7 | 4.8 | 2,300 |
| With APRI-1.5 | 1.9 | 4.0 | 6.0 | 8.1 | 10.2 | 4,900 |
| With FIB4-0.6 | 0.2 | 0.4 | 0.7 | 0.9 | 1.2 | 590 |
| With FIB4-1.0 | 0.4 | 0.8 | 1.4- | 2.0 | 2.6 | 1,300 |
| F3-scenario | | | | | | |
| With perfect test | 0.1 | 0.9 | 1.9 | 3.2 | 4.6 | 2,200 |
| With FibroScan | 1.1 | 2.5 | 4.0 | 5.6 | 7.2 | 3,500 |
| With patented blood biomarkers | 0.8 | 1.8 | 2.9 | 4.0 | 5.3 | 2,500 |
| With FIB4-1.45 | 0.8 | 1.7 | 2.7 | 3.9 | 5.0 | 2,400 |
| With FIB4-3.25 | 2.0 | 4.2 | 6.3 | 8.5 | 10.6 | 5,100 |
| Universal treatment | 0.1 | 0.3 | 0.4 | 0.6 | 0.7 | 350 |
| Cumulated incidence of liver complications | % | % | % | % | % | N* |
| No treatment | 1.6 | 3.2 | 4.8 | 6.5 | 8.2 | 4,600 |
| With useless test† | 1.0 | 1.9 | 2.9 | 3.9 | 4.9 | 2,700 |
| F2-scenario | | | | | | |
| With perfect test | 0.3 | 0.6 | 1.0 | 1.3 | 1.6 | 920 |
| With FibroScan | 0.4 | 0.7 | 1.2 | 1.7 | 2.3 | 1,300 |
| With patented blood biomarkers | 0.4 | 0.8 | 1.2 | 1.7 | 2.2 | 1,200 |

| | | | | | | |
|---|---|---|---|---|---|---|
| With APRI-0.5 | 0.4 | 0.9 | 1.4 | 2.0 | 2.6 | 1,500 |
| With APRI-1.5 | 1.0 | 2.1 | 3.3 | 4.5 | 5.7 | 3,200 |
| With FIB4-0.6 | 0.3 | 0.7 | 1.0 | 1.3 | 1.7 | 940 |
| With FIB4-1.0 | 0.4 | 0.8 | 1.2 | 1.7 | 2.1 | 1,200 |
| F3-scenario | | | | | | |
| With perfect test | 0.3 | 0.6 | 1.0 | 1.5 | 2.1 | 1,200 |
| With FibroScan | 0.4 | 0.9 | 1.4 | 2.1 | 2.9 | 1,600 |
| With patented blood biomarkers | 0.4 | 0.9 | 1.4 | 2.0 | 2.6 | 1,500 |
| With FIB4-1.45 | 0.5 | 1.0 | 1.6 | 2.2 | 2.8 | 1,600 |
| With FIB4-3.25 | 1.1 | 2.2 | 3.4 | 4.7 | 6.0 | 3,400 |
| Universal treatment | 0.3 | 0.6 | 1.0 | 1.3 | 1.6 | 880 |
| Cumulated incidence of liver deaths | % | % | % | % | % | N* |
| No treatment | 0.1 | 1.0 | 1.0 | 3.1 | 4.3 | 2,400 |
| With useless test† | 0.1 | 0.6 | 1.2 | 1.9 | 2.6 | 1,500 |
| F2-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.5 | 0.7 | 1.0 | 550 |
| With FibroScan | 0.1 | 0.3 | 0.6 | 0.9 | 1.2 | 700 |
| With patented blood biomarkers | 0.1 | 0.3 | 0.6 | 0.9 | 1.2 | 690 |
| With APRI-0.5 | 0.1 | 0.4 | 0.6 | 1.0 | 1.4 | 790 |
| With APRI-1.5 | 0.1 | 0.7 | 1.3 | 2.1 | 3.0 | 1,700 |
| With FIB4-0.6 | 0.1 | 0.3 | 0.5 | 0.8 | 1.0 | 570 |
| With FIB4-1.0 | 0.1 | 0.3 | 0.6 | 0.9 | 1.2 | 690 |
| F3-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.5 | 0.8 | 1.1 | 630 |
| With FibroScan | 0.1 | 0.3 | 0.6 | 1.0 | 1.5 | 840 |
| With patented blood biomarkers | 0.1 | 0.4 | 0.6 | 1.0 | 1.4 | 790 |
| With FIB4-1.45 | 0.1 | 0.4 | 0.7 | 1.1 | 1.5 | 870 |
| With FIB4-3.25 | 0.1 | 0.7 | 1.4 | 2.2 | 3.1 | 1,800 |
| Universal treatment | 0.1 | 0.3 | 0.5 | 0.7 | 1.0 | 550 |

*Numbers were rounded to ten (for the hundreds) or hundred (for the thousands);†Test with no accuracy to diagnose fibrosis that would result in treating 50% of the population whatever the real stage of fibrosis

Table 3 – Cumulated incidence of clinical outcomes over 5 years (%) and at 5 years (N) in France according to different diagnostic methods of fibrosis and different therapeutic strategies with yearly assessment of fibrosis: no treatment, targeted therapy with F2-scenario, targeted therapy with F3-scenario, and universal treatment.

| | Time from first fibrosis evaluation (years) | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Cumulated incidence of cirrhosis | % | % | % | % | % | N* |
| No treatment | 2.5 | 5.0 | 7.5 | 10.0 | 12.4 | 6,000 |
| With useless test† | 1.3 | 2.1 | 2.5 | 2.8 | 3.0 | 1,500 |
| F2-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.4 | 0.6 | 0.7 | 350 |
| With FibroScan | 0.6 | 0.9 | 1.1 | 1.3 | 1.4 | 690 |
| With patented blood biomarkers | 0.5 | 0.8 | 1.0 | 1.2 | 1.3 | 640 |
| With APRI-0.5 | 0.8 | 1.2 | 1.4 | 1.7 | 1.9 | 900 |
| With APRI-1.5 | 1.9 | 3.5 | 4.9 | 6.0 | 7.1 | 3,400 |
| With FIB4-0.6 | 0.2 | 0.3 | 0.5 | 0.6 | 0.8 | 370 |
| With FIB4-1.0 | 0.4 | 0.5 | 0.7 | 0.8 | 1.0 | 480 |
| F3-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.4 | 0.6 | 0.7 | 350 |
| With FibroScan | 1.1 | 1.8 | 2.3 | 2.7 | 3.0 | 1,500 |
| With patented blood biomarkers | 0.8 | 1.2 | 1.5 | 1.7 | 2.0 | 950 |
| With FIB4-1.45 | 0.8 | 1.1 | 1.4 | 1.6 | 1.8 | 890 |
| With FIB4-3.25 | 2.0 | 3.8 | 5.3 | 6.6 | 7.9 | 3,800 |
| Universal treatment | 0.1 | 0.3 | 0.4 | 0.6 | 0.7 | 350 |
| Cumulated incidence of liver complications | % | % | % | % | % | N* |
| No treatment | 1.6 | 3.2 | 4.8 | 6.5 | 8.2 | 4,600 |
| With useless test† | 1.0 | 1.6 | 2.1 | 2.5 | 2.8 | 1,600 |
| F2-scenario | | | | | | |
| With perfect test | 0.3 | 0.6 | 1.0 | 1.3 | 1.6 | 880 |
| With FibroScan | 0.4 | 0.7 | 1.0 | 1.3 | 1.6 | 910 |
| With patented blood biomarkers | 0.4 | 0.7 | 1.0 | 1.3 | 1.6 | 920 |

| | | | | | | |
|---|---|---|---|---|---|---|
| With APRI-0.5 | 0.4 | 0.8 | 1.1 | 1.4 | 1.7 | 960 |
| With APRI-1.5 | 1.0 | 1.8 | 2.4 | 2.9 | 3.4 | 1,900 |
| With FIB4-0.6 | 0.3 | 0.7 | 1.0 | 1.3 | 1.6 | 890 |
| With FIB4-1.0 | 0.4 | 0.7 | 1.0 | 1.4 | 1.7 | 930 |
| F3-scenario | | | | | | |
| With perfect test | 0.3 | 0.6 | 1.0 | 1.3 | 1.6 | 880 |
| With FibroScan | 0.4 | 0.7 | 1.1 | 1.4 | 1.7 | 970 |
| With patented blood biomarkers | 0.4 | 0.7 | 1.1 | 1.4 | 1.7 | 960 |
| With FIB4-1.45 | 0.5 | 0.8 | 1.2 | 1.5 | 1.8 | 1,000 |
| With FIB4-3.25 | 1.1 | 1.9 | 2.6 | 3.1 | 3.7 | 2,100 |
| Universal treatment | 0.3 | 0.6 | 1.0 | 1.3 | 1.6 | 880 |
| Cumulated incidence of liver deaths | % | % | % | % | % | N* |
| No treatment | 0.1 | 1.0 | 2.0 | 3.1 | 4.3 | 2,400 |
| With useless test† | 0.1 | 0.6 | 1.1 | 1.5 | 1.8 | 1,000 |
| F2-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.5 | 0.7 | 1.0 | 540 |
| With FibroScan | 0.1 | 0.3 | 0.5 | 0.8 | 1.0 | 570 |
| With patented blood biomarkers | 0.1 | 0.3 | 0.5 | 0.8 | 1.0 | 570 |
| With APRI-0.5 | 0.1 | 0.4 | 0.6 | 0.8 | 1.1 | 600 |
| With APRI-1.5 | 0.1 | 0.7 | 1.2 | 1.6 | 2.1 | 1,200 |
| With FIB4-0.6 | 0.1 | 0.3 | 0.5 | 0.7 | 1.0 | 550 |
| With FIB4-1.0 | 0.1 | 0.3 | 0.6 | 0.8 | 1.0 | 580 |
| F3-scenario | | | | | | |
| With perfect test | 0.1 | 0.3 | 0.5 | 0.7 | 2.0 | 550 |
| With FibroScan | 0.1 | 0.3 | 0.6 | 0.8 | 1.1 | 600 |
| With patented blood biomarkers | 0.1 | 0.4 | 0.6 | 0.8 | 1.1 | 600 |
| With FIB4-1.45 | 0.1 | 0.4 | 0.6 | 0.9 | 1.1 | 630 |
| With FIB4-3.25 | 0.1 | 0.7 | 1.2 | 1.7 | 2.2 | 1,300 |
| Universal treatment | 0.1 | 0.3 | 0.5 | 0.7 | 1.0 | 550 |

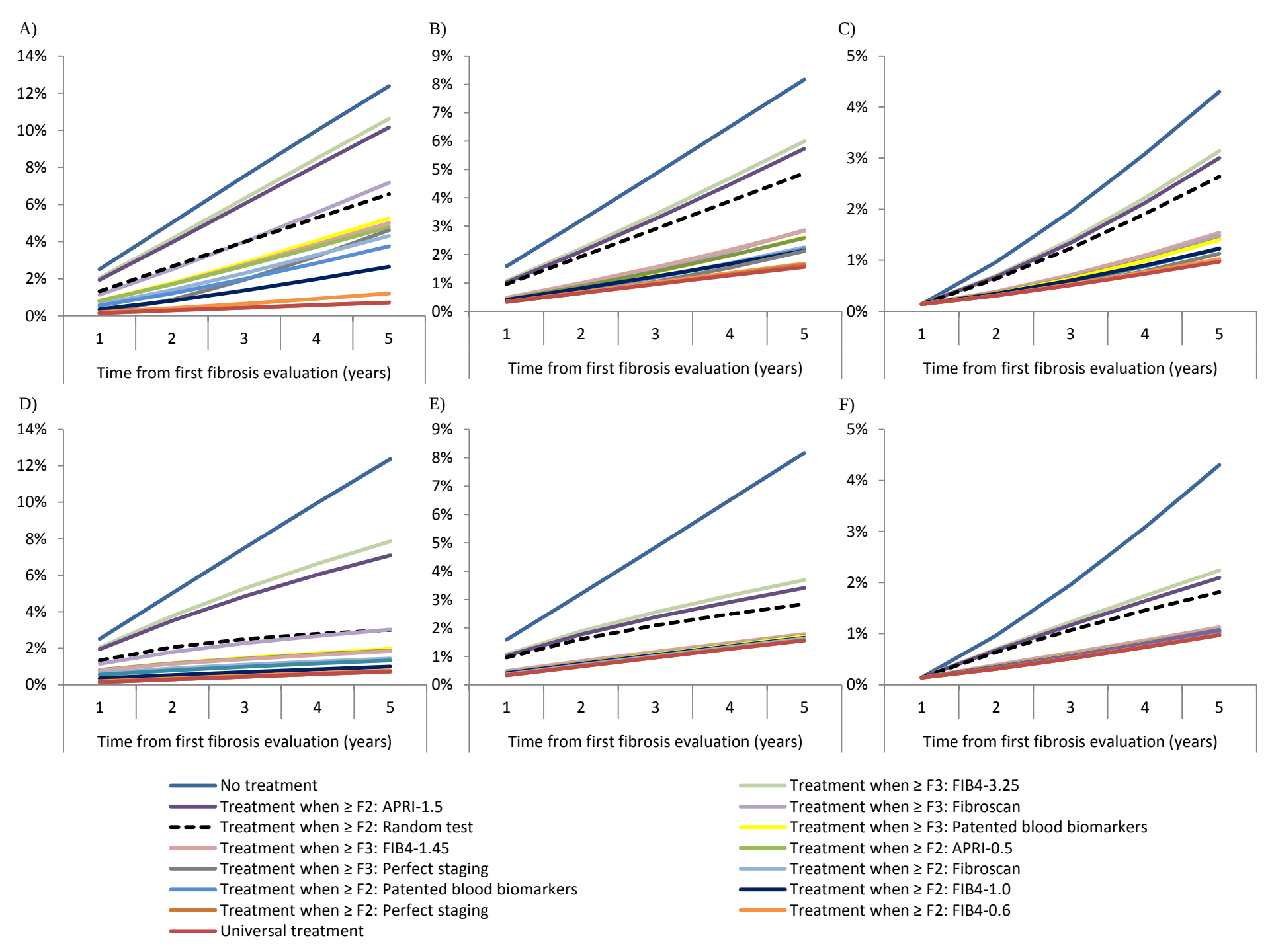
*Numbers were rounded to ten (for the hundreds) or hundred (for the thousands);†Test with no accuracy to diagnose fibrosis that would result in treating 50% of the population whatever the real stage of fibrosis

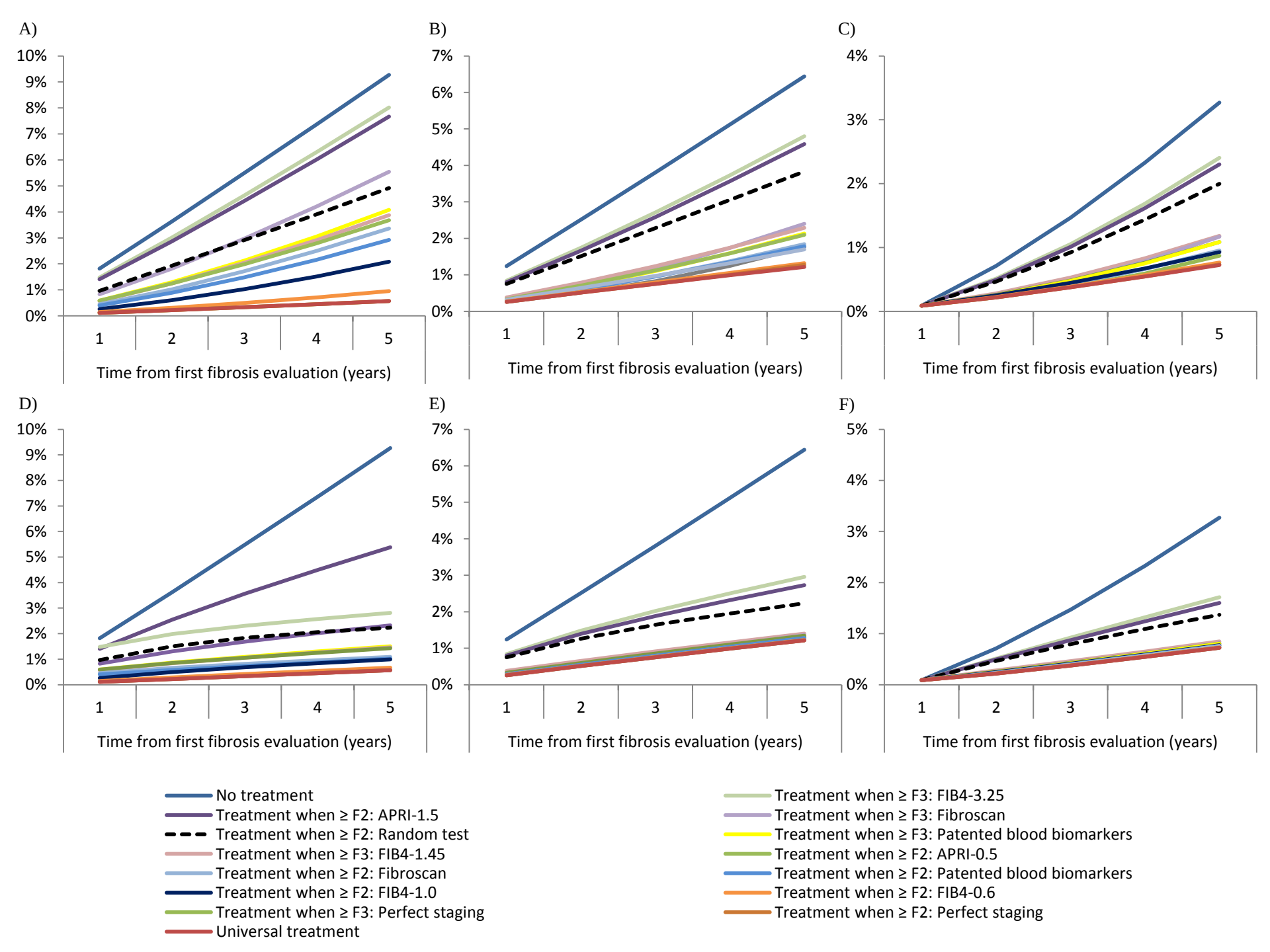
**Figure legends**

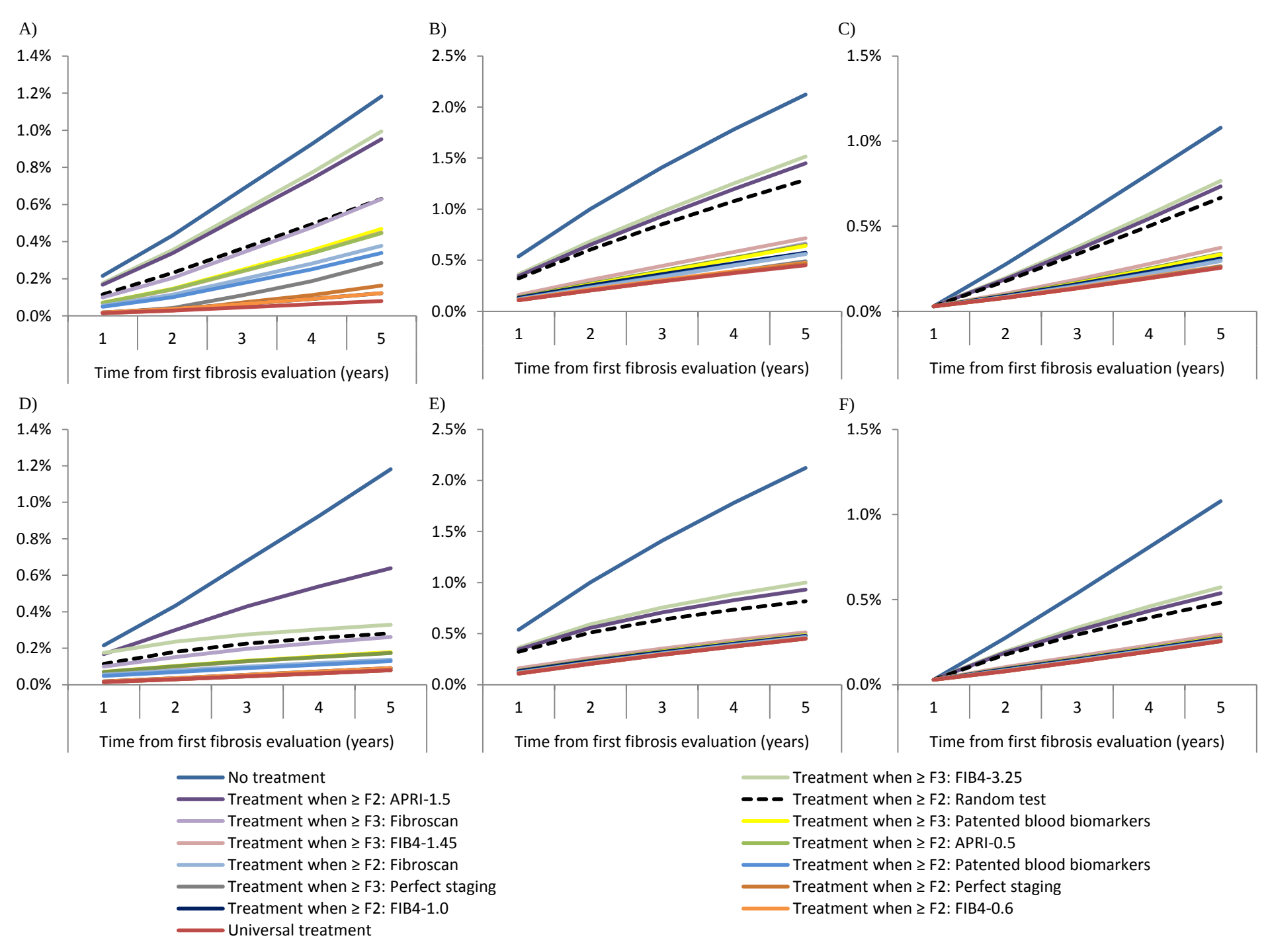
Figure 1: Cumulated incidence of clinical outcomes over 5 years in France according to different diagnostic methods of fibrosis and different therapeutic strategies. Base-case analysis corresponding to one assessment of fibrosis: (A) HCV-related cirrhosis, (B) liver complications, (C) liver-related deaths; alternative analysis corresponding to yearly assessment of fibrosis: (D) HCV-related cirrhosis, (E) liver complications, (F) liver-related deaths

Figure 2: Cumulated incidence of clinical outcomes over 5 years in Italy according to different diagnostic methods of fibrosis and different therapeutic strategies. Base-case analysis corresponding to one assessment of fibrosis: (A) HCV-related cirrhosis, (B) liver complications, (C) liver-related deaths; alternative analysis corresponding to yearly assessment of fibrosis: (D) HCV-related cirrhosis, (E) liver complications, (F) liver-related deaths

Figure 3: Cumulated incidence of clinical outcomes over 5 years in UK according to different diagnostic methods of fibrosis and different therapeutic strategies. Base-case analysis corresponding to one assessment of fibrosis: (A) HCV-related cirrhosis, (B) liver complications, (C) liver-related deaths; alternative analysis corresponding to yearly assessment of fibrosis: (D) HCV-related cirrhosis, (E) liver complications, (F) liver-related deaths


A)
14%
12%
10%
8%
6%
4%
2%
0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
B)
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
C)
5%
4%
3%
2%
1%
0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
D)
14%
12%
10%
8%
6%
4%
2%
0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
E)
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
F)
5%
4%
3%
2%
1%
0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
No treatment
Treatment when ≥ F2: APRI-1.5
Treatment when ≥ F2: Random test
Treatment when ≥ F3: FIB4-1.45
Treatment when ≥ F3: Perfect staging
Treatment when ≥ F2: Patented blood biomarkers
Treatment when ≥ F2: Perfect staging
Universal treatment
Treatment when ≥ F3: FIB4-3.25
Treatment when ≥ F3: Fibroscan
Treatment when ≥ F3: Patented blood biomarkers
Treatment when ≥ F2: APRI-0.5
Treatment when ≥ F2: Fibroscan
Treatment when ≥ F2: FIB4-1.0
Treatment when ≥ F2: FIB4-0.6


A)
B)
C)
D)
E)
F)
Time from first fibrosis evaluation (years)
No treatment
Treatment when ≥ F2: APRI-1.5
Treatment when ≥ F2: Random test
Treatment when ≥ F3: FIB4-1.45
Treatment when ≥ F2: Fibroscan
Treatment when ≥ F2: FIB4-1.0
Treatment when ≥ F3: Perfect staging
Universal treatment
Treatment when ≥ F3: FIB4-3.25
Treatment when ≥ F3: Fibroscan
Treatment when ≥ F3: Patented blood biomarkers
Treatment when ≥ F2: APRI-0.5
Treatment when ≥ F2: Patented blood biomarkers
Treatment when ≥ F2: FIB4-0.6
Treatment when ≥ F2: Perfect staging


A)
1.4%
1.2%
1.0%
0.8%
0.6%
0.4%
0.2%
0.0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
B)
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
C)
1.5%
1.0%
0.5%
0.0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
D)
1.4%
1.2%
1.0%
0.8%
0.6%
0.4%
0.2%
0.0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
E)
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
F)
1.5%
1.0%
0.5%
0.0%
1
2
3
4
5
Time from first fibrosis evaluation (years)
No treatment
Treatment when ≥ F2: APRI-1.5
Treatment when ≥ F3: Fibroscan
Treatment when ≥ F3: FIB4-1.45
Treatment when ≥ F2: Fibroscan
Treatment when ≥ F3: Perfect staging
Treatment when ≥ F2: FIB4-1.0
Universal treatment
Treatment when ≥ F3: FIB4-3.25
Treatment when ≥ F2: Random test
Treatment when ≥ F3: Patented blood biomarkers
Treatment when ≥ F2: APRI-0.5
Treatment when ≥ F2: Patented blood biomarkers
Treatment when ≥ F2: Perfect staging
Treatment when ≥ F2: FIB4-0.6

Cumulated incidence of clinical outcomes over 5 years in France according to different diagnostic methods of fibrosis and different therapeutic strategies. Panels A, B and C correspond to one assessment of fibrosis during the 5-year period (meaning that patients would not be offered treatment at all during the 5-year period when being diagnosed in stage <F2 or in stage < F3): (A) HCV-related cirrhosis, (B) liver complications, (C) liver-related deaths; panels D, E and F correspond to yearly assessment of fibrosis during the 5-year period (resulting in the initiation of treatment in newly identified patients with significant fibrosis): (D) HCV-related cirrhosis, (E) liver complications, (F) liver-related deaths