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Complete title:

Direct Medical Costs Associated with the Extrahepatic Manifestations of Hepatitis C Infection in Europe

Running Title:

Economic Burden of HCV Extrahepatic Manifestations in the EU5

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Key Words

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Abstract

Commentato [RAB1]: Not to exceed 250 words

Hepatitis C virus (HCV) infection is a systemic disease associated with both hepatic and extrahepatic manifestations (EHM). The burden associated with the hepatic manifestation of HCV infection has been well-documented in Europe; however, the burden of HCV-EHM in Europe remains unknown. The objective of this study was to estimate the annual direct medical costs associated with HCV-EHMs in five European countries. A previously validated economic model was used to estimate the annual direct medical cost associated with HCV-EHMs. Excess prevalence of EHMs in HCV patients relative to that in non-HCV patients were obtained from a recent meta-analysis. Per-patient-per-year (PPPY) inpatient, outpatient and medication costs to treat each EHM were obtained from the literature, national databases, or expert opinion if unavailable otherwise. All costs were adjusted to 2016 euros (€). The overall direct medical costs associated with HCV-EHMs were calculated by multiplying the total PPPY costs of each EHM by the respective excess prevalence rates, and then by the size of the HCV-infected population in each country. The impact of treatment with direct-acting antivirals (DAAs) was explored using HCV-EHM excess prevalence rates among cured patients when compared to untreated HCV patients, as sourced from a meta-analysis. The total annual direct medical cost associated with HCV-EHMs was estimated to be 2.17 billion euro (€), with a per HCV patient cost ranging from be €899 to €1,647 annually. DAA treatment was projected to result in cost savings of €316 million per year. We find that the annual economic burden of EHMs is significant, and may be partly mitigated by treatment with DAAs.

Introduction

Hepatitis C virus (HCV) infection is a systemic disease which is associated with both hepatic and extrahepatic manifestations (EHM). In Europe, over 19 million persons are infected with HCV (1). The clinical and economic consequences of the hepatic manifestations of HCV are well-characterized. These can include progression to cirrhosis, decompensation, hepatocellular carcinoma and liver transplant, significantly impacting patient morbidity and mortality, and contributing substantially to the economic burden of disease (2).

In addition to the hepatic burden of disease, it has been shown that up to 74% of HCV patients may experience EHMs (3). A systematic review identified more than 200 studies documenting the association of various EHMs with HCV (4). A recent meta-analysis has further quantified the excess prevalence of specific EHMs, including type 2 diabetes, B-cell lymphoma, and Sjögren's syndrome, in HCV patients (5). Prior work has shown that the annual economic burden of EHMs of HCV is substantial in the United States and France, at \$1.5 billion (bn) and € 256 million (m), respectively (5, 6). However, the direct medical costs associated with HCV-related EHMs in other European countries remains unknown.

The current standard of care for HCV involves treatment with direct-acting antivirals (DAAs) (7). DAAs have shown excellent safety and tolerability in HCV patients of all genotypes, with sustained virologic response (SVR) rates in excess of 95% in most subpopulations (8, 9) and significant improvements on patient-reported outcomes (10, 11). There is a large number of studies that document the significant morbidity and mortality benefit of achieving SVR in HCV patients at all stages of fibrosis (4). Thus, early treatment with DAAs can prevent a substantial portion of direct medical costs related to downstream hepatic HCV complications (12-18). Treatment of at-risk populations with DAAs has also been projected to reduce viral transmission (19, 20).

Achieving SVR can also lessen the clinical burden of EHMs. Retrospective and prospective studies in several countries have shown that the achievement of SVR may protect against the development of mixed cryoglobulinemia, malignant lymphoma, end-stage renal disease (ESRD) and type 2 diabetes (21-25). Clinical guidelines in Europe therefore recommend that HCV patients with clinically significant EHMs be prioritized for DAA treatment (7, 26). A recent study from France has estimated that DAA treatment may reduce the economic burden of EHMs by up to 13% (6). However, the impact of DAA treatment on the economic burden of EHMs in other countries remains unknown.

The objective of this study was to estimate the annual direct medical costs associated with HCV-related EHMs in the EU5 (France, FRA; Germany, GER; Italy, ITA; United Kingdom, UK; Spain, ESP), and to evaluate the potential impact of HCV treatment with DAAs on this burden.

Materials and methods

A previously validated economic model (5) was adapted to the German, Spanish, Italian, and UK perspectives and used to estimate the annual direct medical cost associated with EHMs of HCV. Estimates from the French perspective were taken from our previously published analysis (6).

Excess prevalence of 13 EHMs (mixed cryoglobulinemia vasculitis, glomerulonephritis (increased creatinine), end-stage renal disease (ESRD), porphyria cutanea tarda, lichen planus, type 2 diabetes mellitus (T2DM), depression,

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rheumatoid-like arthritis, lymphoma, Sjögren syndrome, stroke, heart failure, and myocardial infarction) were obtained directly from a recent systematic review and meta-analysis (5), by subtracting the prevalence of the EHM in the general population from its prevalence in the HCV population.

Per patient per year (PPPY) inpatient, outpatient, and pharmacy resource utilization and costs to treat EHMs in the EU were obtained from the literature (27-52), national databases and fee schedules (53-59), or expert opinion if otherwise unavailable (**Table 1**). All costs were adjusted to 2016 euros (€), using a pound sterling to euro exchange rate of 1.15.

Annual inpatient resource utilization was sourced from the published literature where available (27-52). If unavailable, national databases (hospital episode statistics (HES) in England and the "Conjunto Mínimo Básico de Datos" (CMDDB) in Spain) indexed by ICD-10 codes were used to source the mean length of inpatient hospitalization stay for each EHM (53, 54). The cost of an inpatient episode was calculated by multiplying the mean length of stay by the average cost of a bed day in that country. For Germany and Italy, where we did not have readily accessible length of stay data, the Spanish length of stay data were used and multiplied by the cost of a bed day in each respective country to calculate the cost of an inpatient episode (55). The percentage of HCV patients with each EHM experiencing an inpatient episode annually was sourced from a meta-analysis(5), and multiplied by the episode cost to calculate the PPPY inpatient cost.

Annual outpatient and pharmacy resource utilization for each EHM were sourced via the published literature where available (27-52). Where unavailable, healthcare resource utilization data were collected via expert opinion, and mapped to the national or regional reference costs in each country, using the following fee schedules: Germany, Einheitlicher Bewertungsmaßstab (EBM); Italy, Agenzia Italiana del Farmaco (AIFA); Spain, Andalucía, Osikadetzka, País Vasco, Extremadura, or Illes Balears fee schedules, as sourced from Oblikue eSalud; and UK, National Health Service (NHS) (56-59). It was assumed that 100% of HCV patients with each EHM would use outpatient and pharmacy resources.

The overall national direct medical annual costs associated with each EHM were calculated by multiplying the total PPPY costs of each condition by its respective excessive prevalence rate (**Table 1**), and then by the size of the HCV-infected population in each country, which was sourced from the literature (**Table A-1**).

The impact of DAA treatment and achievement of SVR on the economic burden of EHMs was evaluated by applying the results of a meta-analysis assessing the reduction in EHM prevalence in patients achieving SVR to the calculated healthcare costs of managing each EHM (6). We assumed that all patients receiving DAA treatment would be cured, resulting in a relative reduction in excess prevalence of particular EHMs for which robust evidence for the impact of SVR exists (mixed cryoglobulinemia vasculitis, end-stage renal disease, T2DM, stroke, and myocardial infarction) (21-25).

Sensitivity analysis was performed by considering the 95% confidence intervals for the EHM prevalence rates as reported in the meta-analysis, which was descriptive in nature in that no formal statistical analyses were performed.

Results

Applying the excess prevalence rates of EHMs from the international meta-analysis to country-specific 2016 healthcare costs, we estimated the total annual economic burden of EHMs of HCV in the EU5 to be € 2.17 billion (bn), as detailed in **Table 2**. Annual total medical costs were highest in Italy, and lowest in the UK. Sensitivity analyses based on the 95% confidence intervals of the excess EHM prevalence rates from the meta-analysis projected the direct medical costs associated with HCV-EHMs to range from a low of € 121 m in the UK to a high of € 1,490 m in ITA, and are detailed in **Table 2**. The proportional contribution of each EHM to the projected burden of disease is detailed in **Table A- 2**; the EHMs that contributed most significantly to the overall burden included Sjögren's syndrome, T2DM, CV disease, depression, and glomerulonephritis.

The annual burden of EHMs per HCV patient is projected to be € 1,647, € 1,333, € 1,331, € 1,015 and € 899 in Italy, Germany, France, Spain and the United Kingdom, respectively (**Table A-3**). EHMs contributing most to the per-patient burden are detailed in **Table A- 3** and included Sjögren's syndrome and T2DM.

Based on the assumption that all HCV patients receiving DAA treatment would be cured, the total reduction in costs of managing EHMs attributable to patients achieving SVR varied by country, with annual estimates of cost savings ranging from €22.9 m in the UK to €145.1 m in Italy (**Table 3**). This corresponded to relative savings of 11.3% to 18.7%, depending on the country.

Discussion

Our study estimates that the annual economic burden of extrahepatic manifestations in the EU5 is substantial, adding significantly to the overall burden of HCV infection. Further, we find that treatment with DAAs may lead to a reduction in this burden.

Our study's projections are in line with prior work assessing the economic burden of EHMs in the United States, which has been estimated at \$1.5 billion annually (5). In our study, the magnitude of the annual economic burden varied significantly by country and correlated closely with HCV prevalence, with a high of € 1,093 m in Italy (prevalent HCV population, 664,791) and a low of € 170 m in the United Kingdom (prevalent HCV population, 188,821). The costs per HCV patient per year also varied significantly from country to country, reflecting regional differences in the management of these conditions. For example, rituximab, a relatively expensive monoclonal antibody, was viewed as standard of care for the treatment of Sjögren's syndrome by clinical experts in Italy but not in Germany, with a corresponding impact on the annual per-HCV patient costs of this EHM (€445 vs. €196, respectively). The EHMs with the highest excess prevalence in HCV patients contributed the most to the per HCV patient EHM economic burden. Sjögren's syndrome, T2DM, and depression have excess prevalence in HCV patients of 11.2%, 5.7%, and 7.3%, respectively, and their cost per HCV patient ranged from € 206 to € 534, € 128 to € 270, and € 32 to € 249, respectively, depending on the country.

Our study is one of the first to simulate the impact of DAA treatment on the economic burden of EHMs. The EHMs with the greatest contributions to estimated cost savings upon achievement of SVR were T2DM and mixed

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cryoglobulinemia, given their high rate of excess prevalence in HCV patients and substantial per patient costs. Our projections of SVR leading to decreased direct medical costs for particular EHMs have been validated to a certain extent with real-world data. A study at a tertiary centre in France has shown that when HCV patients with mixed cryoglobulinemia are treated with DAAs, direct medical costs due to hospitalization and non-HCV pharmacy prescriptions decrease, reflecting the lesser need for medical management of this EHM after a patient is cured of HCV (60).

These results add to the growing body of literature emphasizing the importance of the timely treatment of HCV patients with DAAs. There is already clinical consensus that HCV patients with EHMs should be immediately treated (7), and we now provide an additional, economic rationale for doing so. Policy-makers are recognizing this imperative, and, as recent developments from France and Australia demonstrate (61, 62), increasingly recommending that all HCV patients be immediately treated, in the hopes of preventing both hepatic and extra-hepatic manifestations altogether.

Given the increased acquisition cost of DAAs relative to older, less effective regimens for HCV, many health systems have in the past questioned whether DAAs provided adequate value for money. Cost-effectiveness analyses (CEA) seek to place the costs associated with a product in context with its long-term value to the health system. While several models assessing the cost-effectiveness of DAAs in HCV in European countries have been published (12-15), these have focused exclusively on the costs associated with hepatic manifestations of the disease. To our knowledge, no CEA has incorporated the cost savings attributable to the decreased clinical burden of EHMs after DAA treatment. Given the results of our study, the true economic value of DAA regimens in the treatment of HCV have therefore, to date, likely been underestimated.

Our study is not without limitations. Excess prevalence rates were sourced from a meta-analysis that included both primary care and specialist clinic data. As a result, these rates may be an overestimation of the excess prevalence in the general HCV population; to address this limitation, our sensitivity analyses explored the potential impact of lower EHM excess prevalence rates on the economic burden of disease, which remained substantial. The EHM prevalence rates used in our model were international, not country-specific, and sourced from a meta-analysis that aggregated prevalence rates across different years; further research should seek to understand country-specific EHM prevalence. The costs of managing each EHM were not directly available in all countries, and the approximations of resource utilization (for example, using hospitalization length of stay data from Spain to approximate these data for Italian patients) based on expert opinion that we used in our analysis may be subject to bias. There is a lack of clear evidence on whether DAA treatment reduces the excess prevalence and / or severity of all EHMs; in our analysis, we conservatively included only the EHMs with the most robust evidence available for this exploratory analysis, which may have underestimated the true impact of DAA treatment. There is some evidence that the impact of SVR on EHMs can vary by genotype (25), a level of granularity that was not accounted for in our analysis. Finally, our analysis did not stratify EHM costs based on treatment experience, cirrhosis status, or EHM severity, or account for HCV patients that have already been cured by DAAs; further research is warranted to understand the impact of each of these parameters on the overall burden of disease.

In summary, we show that the economic burden associated with the extrahepatic manifestations of HCV in Europe is substantial, and that treatment with DAAs can reduce a considerable portion of these direct medical costs.

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1. Authors' declaration of personal interests:

(i) [Carrión J.A.] has served as a speaker, a consultant and an advisory board member for [Gilead; Abbvie; and MSD], and has received research funding from [names of organization].

(ii) [Anna Linda Zignego] has served as a speaker, a consultant and an advisory board member for BMS, Gilead, Janssen Cilag, MSD, and Abbvie,

(iii) [Name of individual] owns stocks and shares in [name of organization].

(iv) [Name of individual] owns patent [patent identification and brief description].

2. Declaration of funding interests:

(i) This study was funded [in part or in full] by [insert name of funding organization and provide funding identification numbers], grant number [insert grant or other identification number].

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(iii) Initial data analyses were undertaken by [name of individuals if not listed as authors] who are employees of [name company] and received funding from [insert name of funding organization].

(iv) Writing support was provided by [insert name of individual(s)] of [name company] and funded by [insert name of funding organization].

Appendices

Supplemental Material

Table A-1: Population inputs

| | Country population (2016) | HCV viraemic prevalence | HCV population (2016) |
|-----|---------------------------|-------------------------|-----------------------|
| GER | 80,682,000 | 0.25% | 201,705 |
| FRA | 63,030,000 | 0.29% | 186,144 |
| ESP | 46,064,000 | 0.84% | 386,937 |
| ITA | 59,801,000 | 1.11% | 664,791 |
| UK | 65,111,000 | 0.29% | 188,821 |

UK, United Kingdom; FRA, France; GER, Germany; ESP, Spain; ITA, Italy; HCV, hepatitis C virus

Table A-2: Estimation of contribution of individual EHMs to the overall annual costs of extrahepatic manifestation of HCV infection, using rates from international systematic literature review and meta-analysis applied to country-specific healthcare costs

| | GER | ESP | ITA | UK (in EUR) | FRA |
|-------------------------|--------------|--------------|---------------|--------------|--------------|
| Arthritis | € 6,226,633 | € 21,985,094 | € 36,648,543 | € 6,154,672 | € 455,158 |
| CV disease* | € 25,517,542 | € 36,042,779 | € 161,624,569 | € 21,726,086 | € 17,808,976 |
| Depression | € 46,691,647 | € 12,390,573 | € 106,213,561 | € 16,398,748 | € 46,177,221 |
| ESRD | € 4,706,425 | € 5,250,603 | € 16,220,702 | € 2,168,609 | € 2,692,756 |
| Glomerulonephritis | € 25,527,760 | € 73,795,437 | € 154,788,429 | € 9,441,795 | € 14,532,180 |
| Lichen planus | € 1,646,968 | € 5,718,499 | € 5,084,626 | € 841,780 | € 1,067,839 |
| lymphoma | € 6,282,252 | € 2,373,786 | € 44,584,009 | € 1,510,632 | € 2,356,183 |
| Mixed cryoglobulinemia | € 38,435,499 | € 66,666,226 | € 117,531,681 | € 16,480,410 | € 18,351,667 |
| Porphyria cutanea tarda | € 580,497 | € 1,516,155 | € 1,389,671 | € 597,154 | € 263,981 |
| Sjögren's syndrome | € 39,618,520 | € 79,682,105 | € 295,462,784 | € 65,058,976 | € 99,394,789 |
| Stroke | € 19,254,613 | € 16,517,370 | € 40,664,834 | € 4,997,367 | € 5,122,636 |
| T2DM | € 54,414,577 | € 70,655,207 | € 113,275,490 | € 24,328,459 | € 39,617,651 |

UK, United Kingdom; FRA, France; GER, Germany; ESP, Spain; ITA, Italy; ESRD, end-stage renal disease; T2DM, type 2 diabetes mellitus; CV, cardiovascular disease

*Assumes 50% of patients present with heart failure and 50% of patients with myocardial infarction

Table A-3: Estimation of contribution of individual EHMs to the annual per-HCV patient costs of extrahepatic manifestation of HCV infection, using rates from international systematic literature review and meta-analysis applied to country-specific healthcare costs

| | GER | ESP | ITA | UK | FRA |
|-------------------------|----------|----------|----------|----------|----------|
| Porphyria cutanea tarda | € 2.88 | € 3.92 | € 2.09 | € 3.16 | € 1.42 |
| Lichen planus | € 8.17 | € 14.78 | € 7.66 | € 4.46 | € 5.74 |
| ESRD | € 23.33 | € 13.57 | € 24.44 | € 11.48 | € 14.47 |
| Arthritis | € 30.87 | € 56.82 | € 55.21 | € 32.60 | € 2.45 |
| lymphoma | € 31.15 | € 6.13 | € 67.17 | € 8.00 | € 12.66 |
| Stroke | € 95.46 | € 42.69 | € 61.26 | € 26.47 | € 27.52 |
| Mixed cryoglobulinemia | € 190.55 | € 172.29 | € 177.06 | € 87.28 | € 98.59 |
| T2DM | € 269.77 | € 182.60 | € 170.65 | € 128.84 | € 212.83 |
| CV disease* | € 126.51 | € 93.15 | € 243.49 | € 115.06 | € 95.67 |

| | | | | | |
|--------------------------|------------------|------------------|------------------|-----------------|------------------|
| Glomerulonephritis | € 126.56 | € 233.19 | € 164.00 | € 50.00 | € 78.07 |
| Depression | € 231.48 | € 32.02 | € 160.01 | € 86.85 | € 248.07 |
| Sjögren's syndrome | € 196.42 | € 205.93 | € 445.11 | € 344.55 | € 533.97 |
| Total per patient | € 1333.15 | € 1014.62 | € 1647.34 | € 775.02 | € 1331.39 |

UK, United Kingdom; FRA, France; GER, Germany; ESP, Spain; ITA, Italy; ESRD, end-stage renal disease; T2DM, type 2 diabetes mellitus; CV, cardiovascular disease

*Assumes 50% of patients present with heart failure and 50% of patients with myocardial infarction

Tables

Table 1: Prevalence rates and yearly costs associated with extrahepatic manifestations of HCV infection, by country

| | Excess Prevalence in HCV | GER | FRA | ESP | ITA | UK* |
|-------------------------|---|------------|------------|------------|------------|------------|
| Arthritis | 0.90% | € 3,430 | € 272 | € 6,313 | € 6,135 | £3,123 |
| Depression | 7.30% | € 3,171 | € 3,398 | € 439 | € 2,192 | £1,026 |
| ESRD | 0.04% | € 58,333 | € 36,165 | € 33,924 | € 61,091 | £24,759 |
| Glomerulonephritis | 1.8% | € 4,219 | € 2,602 | € 6,357 | € 7,773 | £1,691 |
| Heart failure | 1.80% | € 3,434 | € 3,770 | € 5,166 | € 11,494 | £472 |
| Lichen planus | 0.80% | € 1,021 | € 717 | € 1,847 | € 957 | £481 |
| Lymphoma | 0.14% | € 22,247 | € 9,041 | € 4,382 | € 47,976 | £4,914 |
| MI | 1.80% | € 10,623 | € 6,860 | € 5,184 | € 15,560 | £6,851 |
| Mixed cryoglobulinemia | 4.90% | € 3,889 | € 2,012 | € 3,516 | € 3,613 | £1,536 |
| Porphyria cutanea tarda | 0.50% | € 576 | € 284 | € 784 | € 419 | £545 |
| Sjögren's syndrome | 11.20% | € 1,754 | € 4,768 | € 1,839 | € 3,974 | £2,653 |
| Stroke | 0.50% | € 19,092 | € 5,504 | € 8,537 | € 12,252 | £4,564 |
| T2DM | 5.70% | € 4,733 | € 3,734 | € 3,204 | € 2,994 | £1,949 |

UK, United Kingdom; FRA, France; GER, Germany; ESP, Spain; ITA, Italy; ESRD, end-stage renal disease; T2DM, type 2 diabetes mellitus; MI, myocardial infarction

*UK inputs were converted to Euros at an exchange rate of 1.15 prior to use in the economic model

Table 2: Estimation of total annual costs associated with extrahepatic manifestation of HCV infection, using rates from international systematic literature review and meta-analysis applied to country-specific healthcare costs

| | Annual economic burden | Low estimate | High estimate |
|--------------|-------------------------------|------------------------|------------------------|
| UK | € 169,704,687 | € 121,188,466 | € 229,382,234 |
| FRA | € 247,841,039 | € 172,781,187 | € 339,479,444 |
| GER | € 268,902,933 | € 182,037,995 | € 379,108,073 |
| ESP | € 392,593,834 | € 292,719,613 | € 524,589,582 |
| ITA | € 1,093,488,898 | € 769,191,406 | € 1,489,945,967 |
| TOTAL | € 2,103,169,366 | € 1,485,053,426 | € 2,874,106,819 |

UK, United Kingdom; FRA, France; GER, Germany; ESP, Spain; ITA, Italy;

Table 3: Estimation of total reduction in annual costs associated with extrahepatic manifestation of HCV infection, assuming all treated patients are cured

| | FRA | ESP | ITA | GER | UK |
|------|--------------|--------------|--------------|--------------|-------------|
| T2DM | € 14,005,942 | € 24,128,753 | € 38,683,580 | € 18,582,578 | € 8,308,169 |

| | | | | | |
|------------------------|---------------------|---------------------|----------------------|---------------------|---------------------|
| Mixed cryoglobulinemia | € 8,683,977 | € 30,473,132 | € 53,723,731 | € 17,568,866 | € 7,533,195 |
| MI | € 2,643,785 | € 5,810,333 | € 27,522,350 | € 4,908,364 | € 3,822,495 |
| ESRD | € 2,427,717 | € 4,572,750 | € 14,126,609 | € 4,098,825 | € 1,888,642 |
| Stroke | € 1,444,554 | € 4,499,332 | € 11,077,101 | € 5,244,957 | € 1,361,283 |
| TOTAL | € 29,205,975 | € 69,484,300 | € 145,133,371 | € 50,403,591 | € 22,913,784 |

UK, United Kingdom; FRA, France; GER, Germany; ESP, Spain; ITA, Italy; ESRD, end-stage renal disease; T2DM, type 2 diabetes mellitus; MI, myocardial infarction

References

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013;57(4):1333-42.
2. El Khoury AC, Wallace C, Klimack WK, Razavi H. Economic burden of hepatitis C-associated diseases: Europe, Asia Pacific, and the Americas. *Journal of medical economics*. 2012;15(5):887-96.
3. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis and rheumatism. 1999;42(10):2204-12.
4. Nuno Solinis R, Arratibel Ugarte P, Rojo A, Sanchez Gonzalez Y. Value of Treating All Stages of Chronic Hepatitis C: A Comprehensive Review of Clinical and Economic Evidence. *Infectious diseases and therapy*. 2016;5(4):491-508.
5. Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology*. 2016;150(7):1599-608.
6. Cacoub PV, M.; Desbois, A.; Younossi, Z. Direct Medical Costs Associated with the Extrahepatic Manifestations of Hepatitis C virus Infection in France Submitted. 2017.
7. European Association for Study of L. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *Journal of hepatology*. 2014;60(2):392-420.
8. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *The New England journal of medicine*. 2015;373(27):2608-17.
9. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *The New England journal of medicine*. 2015;373(27):2599-607.
10. Younossi ZM, Stepanova M, Feld J, Zeuzem S, Sulkowski M, Foster GR, et al. Sofosbuvir and Velpatasvir Combination Improves Patient-reported Outcomes for Patients With HCV Infection, Without or With Compensated or Decompensated Cirrhosis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2017;15(3):421-30 e6.
11. Younossi ZM, Stepanova M, Henry L, Nader F, Hunt S. An In-Depth Analysis of Patient-Reported Outcomes in Patients With Chronic Hepatitis C Treated With Different Anti-Viral Regimens. *The American journal of gastroenterology*. 2016;111(6):808-16.
12. Buti M, Dominguez-Hernandez R, Oyaguez I, Casado MA, Esteban R. Cost-effectiveness analysis of ledipasvir/sofosbuvir in patients with chronic hepatitis C: Treatment of patients with absence or mild fibrosis compared to patients with advanced fibrosis. *Journal of viral hepatitis*. 2017.
13. Stahmeyer JT, Rossol S, Liersch S, Guerra I, Krauth C. Cost-Effectiveness of Treating Hepatitis C with Sofosbuvir/Ledipasvir in Germany. *PLoS one*. 2017;12(1):e0169401.

14. Howells R, Trehan C. Cost-Effectiveness of Ledipasvir/Sofosbuvir for the Treatment of Genotype 1 Or 4 Chronic Hepatitis C in England and Wales. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2015;18(7):A589.
15. Leleu H, Blachier M, Hauvespre A, Pentel J. Cost-Effectiveness of Sofosbuvir and Ledipasvir In The Treatment of Patients With Hepatitis C. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2015;18(7):A585.
16. Felix J, Almeida J, Ferreira D, Mota M, Afonso-Silva M, Silva P, et al. Ledipasvir / Sofosbuvir for The Treatment of Chronic Hepatitis C: A Cost-Effectiveness Analysis Across Different Genotype 1 Clinical Subgroups. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2015;18(7):A585.
17. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Annals of internal medicine*. 2015;162(6):397-406.
18. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. *Alimentary pharmacology & therapeutics*. 2015;41(6):544-63.
19. Lima VD, Rozada I, Grebely J, Hull M, Lourenco L, Nosyk B, et al. Are Interferon-Free Direct-Acting Antivirals for the Treatment of HCV Enough to Control the Epidemic among People Who Inject Drugs? *PloS one*. 2015;10(12):e0143836.
20. Hickman M, De Angelis D, Vickerman P, Hutchinson S, Martin NK. Hepatitis C virus treatment as prevention in people who inject drugs: testing the evidence. *Current opinion in infectious diseases*. 2015;28(6):576-82.
21. Cacoub P, Lidove O, Maisonneuve T, Duhaut P, Thibault V, Ghillani P, et al. Interferon-alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis and rheumatism*. 2002;46(12):3317-26.
22. Hsu YC, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology*. 2014;59(4):1293-302.
23. Hsu YH, Hung PH, Muo CH, Tsai WC, Hsu CC, Kao CH. Interferon-Based Treatment of Hepatitis C Virus Infection Reduces All-Cause Mortality in Patients With End-Stage Renal Disease: An 8-Year Nationwide Cohort Study in Taiwan. *Medicine*. 2015;94(47):e2113.
24. Cacoub P, Ratzliff V, Myers RP, Ghillani P, Piette JC, Moussalli J, et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. *Journal of hepatology*. 2002;36(6):812-8.
25. Thompson AJ, Patel K, Chuang WL, Lawitz EJ, Rodriguez-Torres M, Rustgi VK, et al. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. *Gut*. 2012;61(1):128-34.

26. Zignego AL, Ramos-Casals M, Ferri C, Saadoun D, Arcaini L, Roccatello D, et al. International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. *Autoimmunity reviews*. 2017;16(5):523-41.
27. Corrao G, Ghirardi A, Ibrahim B, Merlino L, Maggioni AP. Burden of new hospitalization for heart failure: a population-based investigation from Italy. *European journal of heart failure*. 2014;16(7):729-36.
28. Roggeri A, Gnani R, Dalmaso M, Rusciani R, Giammaria M, Anselmino M, et al. Resource consumption and healthcare costs of acute coronary syndrome: a retrospective observational administrative database analysis. *Critical pathways in cardiology*. 2013;12(4):204-9.
29. Fattore G, Torbica A, Susi A, Giovanni A, Benelli G, Gozzo M, et al. The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC neurology*. 2012;12:137.
30. Furneri G, Iannazzo S, Berti V, Fregonara Medici M, Parisi S, Fusaro E. The Cost of Rheumatoid Diseases In Italy: Analysis From An Italian Administrative Database. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2015;18(7):A642.
31. Delgado JF, Oliva J, Llano M, Pascual-Figal D, Grillo JJ, Comin-Colet J, et al. Health care and nonhealth care costs in the treatment of patients with symptomatic chronic heart failure in Spain. *Revista espanola de cardiologia*. 2014;67(8):643-50.
32. Salvador-Carulla L, Bendeck M, Fernandez A, Alberti C, Sabes-Figuera R, Molina C, et al. Costs of depression in Catalonia (Spain). *Journal of affective disorders*. 2011;132(1-2):130-8.
33. Mata-Cases M, Casajuana M, Franch-Nadal J, Casellas A, Castell C, Vinagre I, et al. Direct medical costs attributable to type 2 diabetes mellitus: a population-based study in Catalonia, Spain. *The European journal of health economics : HEPAC : health economics in prevention and care*. 2016;17(8):1001-10.
34. Villa G, Rodriguez-Carmona A, Fernandez-Ortiz L, Cuervo J, Rebollo P, Otero A, et al. Cost analysis of the Spanish renal replacement therapy programme. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2011;26(11):3709-14.
35. Biermann J, Neumann T, Angermann CE, Erbel R, Maisch B, Pittrow D, et al. Economic burden of patients with various etiologies of chronic systolic heart failure analyzed by resource use and costs. *International journal of cardiology*. 2012;156(3):323-5.
36. Kirchhoff T, Ruof J, Mittendorf T, Rühl M, Bernateck M, Mau W, et al. Cost of illness in rheumatoid arthritis in Germany in 1997-98 and 2002: cost drivers and cost savings. *Rheumatology*. 2011;50(4):756-61.
37. Wagner CJ, Metzger FG, Sievers C, Marschall U, L'Hoest H, Stollenwerk B, et al. Depression-related treatment and costs in Germany: Do they change with comorbidity? A claims data analysis. *Journal of affective disorders*. 2016;193:257-66.

38. Abbas S, Ihle P, Hein R, Schubert I. [Rehabilitation in geriatric patients after ischemic stroke--a comparison of 2 organisational systems in Germany using claims data of a statutory health insurance fund]. *Die Rehabilitation*. 2013;52(6):375-82.
39. Baumeister SE, Boger CA, Kramer BK, Doring A, Eheberg D, Fischer B, et al. Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. *American journal of nephrology*. 2010;31(3):222-9.
40. Callaghan R, Prabu A, Allan RB, Clarke AE, Sutcliffe N, Pierre YS, et al. Direct healthcare costs and predictors of costs in patients with primary Sjogren's syndrome. *Rheumatology*. 2007;46(1):105-11.
41. Danese MD, Gleeson M, Kutikova L, Griffiths RI, Azough A, Khunti K, et al. Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. *BMJ open*. 2016;6(8):e011805.
42. Brilleman SL, Purdy S, Salisbury C, Windmeijer F, Gravelle H, Hollinghurst S. Implications of comorbidity for primary care costs in the UK: a retrospective observational study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2013;63(609):e274-82.
43. Cognet M, Druais S, Gervais F, Gauthier A, Abrams KR. Cost of Previously Treated Chronic Lymphocytic Leukemia (CLL) and Indolent Non-Hodgkin's Lymphoma (INHL) in the United Kingdom (UK). *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2014;17(7):A549.
44. Byford S, Barrett B, Despiegel N, Wade A. Impact of treatment success on health service use and cost in depression: longitudinal database analysis. *Pharmacoeconomics*. 2011;29(2):157-70.
45. Jones S, Castell C, Goday A, Smith HT, Nicolay C, Simpson A, et al. Increase in direct diabetes-related costs and resource use in the 6 months following initiation of insulin in patients with type 2 diabetes in five European countries: data from the INSTIGATE study. *ClinicoEconomics and outcomes research : CEOR*. 2012;4:383-93.
46. Muller N, Heller T, Freitag MH, Gerste B, Haupt CM, Wolf G, et al. Healthcare utilization of people with type 2 diabetes in Germany: an analysis based on health insurance data. *Diabetic medicine : a journal of the British Diabetic Association*. 2015;32(7):951-7.
47. Alvarez-Sabin J, Quintana M, Masjuan J, Oliva-Moreno J, Mar J, Gonzalez-Rojas N, et al. Economic impact of patients admitted to stroke units in Spain. *The European journal of health economics : HEPAC : health economics in prevention and care*. 2017;18(4):449-58.
48. Kent S, Schlackow I, Lozano-Kuhne J, Reith C, Emberson J, Haynes R, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC nephrology*. 2015;16:65.
49. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2012;27 Suppl 3:iii73-80.

50. Icks A, Haastert B, Gandjour A, Chernyak N, Rathmann W, Giani G, et al. Costs of dialysis--a regional population-based analysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2010;25(5):1647-52.
51. Reinhold TL, C.; Willich, S.; Bruggenjuren, B. The costs of myocardial infarction—a longitudinal analysis using data from a large German health insurance company. *Journal of Public Health*. 2011;19(6):579-86.
52. Cichetti A, Ruggeri M, Codella P, Ridolfi A. The health and social costs of chronic kidney disease in Italy. *Farneconomia e percorsi terapeutici* 2011;12(1):21-8.
53. NHS Digital. Hospital Episode Statistics, Admitted Patient Care - England, 2011-12. <http://content.digital.nhs.uk/catalogue/PUB08288>. Accessed 1 November 2016.
54. Ministerio de Sanidad Servicios Sociales e Igualdad. Conjunto Mínimo Básico de Datos - Catálogo Nacional de Hospitales - Año 2014. <https://www.msssi.gob.es/estadisticas/microdatos.do>. Accessed 1 November 2016.
55. World Health Organization. Health service delivery costs. http://www.who.int/choice/cost-effectiveness/inputs/health_service/en/. Accessed 1 November 2016.
56. Kassenärztliche Bundesvereinigung. Einheitlicher Bewertungsmaßstab (EBM). <http://www.kbv.de/html/ebm.php>. Accessed 1 November 2016.
57. Oblikue. eSalud - Información económica del sector sanitario. <http://esalud.oblikue.com/>. Accessed 1 November 2016.
58. Department of Health. NHS reference costs 2015 to 2016. <https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016>. Accessed 1 November 2016.
59. Agenzia Italiana del Farmaco. Supplemento ordinario n. 8 alla GAZZETTA UFFICIALE. <http://www.trovanorme.salute.gov.it/norme/renderPdf.spring?seriegu=SG&datagu=28/01/2013&redaz=13A00528&artp=3&art=1&subart=1&subart1=10&vers=1&prog=001>. Accessed 1 November 2016.
60. Cacoub P, Vautier M, Desbois AC, Lafuma A, Saadoun D. Effectiveness and cost of hepatitis C virus cryoglobulinaemia vasculitis treatment: From interferon-based to direct-acting antivirals era. *Liver international : official journal of the International Association for the Study of the Liver*. 2017;doi: 10.1111/liv.13465. [Epub ahead of print].
61. ABC. Federal Government to spend \$1 billion on groundbreaking Hepatitis C treatments. <http://www.abc.net.au/news/2015-12-20/federal-government-spending-1billion-on-hepatitis-c-treatment/7043624>. Accessed 7 June 2017.
62. IHS. French government proposes "universal" access to new HCV medicines. <http://www.ihs.com/country-industry-forecasting.html?ID=10659114512>. Accessed 7 June 2017.