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Evaluation of Sustained Virologic Response as a Relevant Surrogate Endpoint for Long-term Outcomes of Hepatitis C Virus Infection

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(See the Editorial Commentary by Suk-Fong Lok on pages 787–8.)

Background. The causal link of sustained virologic response (SVR) with outcome has been challenged. With improved SVR rates with direct-acting antivirals (DAAs), the benefit of SVR would be expected to diminish if the association with outcome is not causal.

Methods. Data were collected for patients starting treatment with interferon (IFN) or DAAs between June 2006 and December 2016. To control for disease severity, criteria for the IDEAL (Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy) trial determined IFN-eligibility. Clinical events were decompensation, hepatocellular carcinoma, liver transplantation, and all-cause mortality.

Results. In 1078 IDEAL-eligible patients, 1306 treatments occurred (52% IFN, 49% DAAs). Cirrhosis was present in 30% DAAs vs 21% IFN ($P < .001$). SVR was 97% with DAAs vs 52% with IFN ($P < .0001$). The 24-month cumulative event-free survival was 99% for IFN and 97% for DAAs with SVR ($P = .08$) and 96% and 75%, respectively, for non-SVR ($P = .01$). SVR was associated with improved event-free survival with an adjusted hazard ratio of 0.21 (95% confidence interval, .06–.71; $P = .01$). Using inverse probability of treatment weighting to match IFN nonresponders with DAA-treated patients, the 24-month event-rate was 1.1% with DAAs compared to 3.4% in IFN nonresponders ($P = .005$), highlighting the clinical benefit of maximizing SVR.

Conclusions. In IFN-eligible patients, SVR is more commonly achieved with DAAs and confers a similar clinical benefit as in those treated with IFN. The reduced event-rate with DAAs compared to IFN, despite similar disease severity, confirm that SVR alters prognosis leading to improved clinical outcomes.

Keywords. hepatitis C virus; sustained virologic response; survival; direct-acting antivirals; interferon.

Chronic hepatitis C virus (HCV) infection remains a major global public health problem with an estimated 71 million people infected [1]. HCV leads to slowly progressive liver injury that may result in long-term complications such as cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and death [2]. Although the prevalence of HCV is decreasing, the disease burden will remain due to aging of the affected population, along with increasing incidence of cirrhosis and its complications [3, 4].

Sustained virologic response (SVR) is considered a durable virologic cure, with multiple studies showing that patients who achieve this endpoint continue to have undetectable HCV RNA in the blood with very low rates of late relapse [5–8]. However, some have challenged SVR as a meaningful endpoint, noting that improved clinical outcomes have not been used as endpoints in randomized controlled trials [9]. Indeed, in the short follow-up of randomized controlled registration trials, the Cochrane review found no differences in clinical outcomes in patients with and without SVR after treatment [10].

The alternative is to use observational studies, comparing outcomes between those who achieve SVR and those who do not respond to therapy or were never treated. Many studies like this have shown that those who achieve SVR have lower rates of complications and reduced liver-related and all-cause mortality compared to those who do not respond to therapy or are untreated [2, 11–14].

These results showing improved outcomes with SVR have been challenged, arguing that SVR may actually itself be a facet of a good prognosis [9]. Notably, many predictors of treatment nonresponse to interferon (IFN)–based therapy are also predictors of worse clinical outcome, making it hard to separate

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the cause and consequence. The introduction of direct-acting antivirals (DAAs) has revolutionized treatment for HCV, leading to SVR rates consistently > 95% compared to SVR rates of 40%–60% with IFN-based therapy [15–19].

The high SVR rates achieved with DAAs provide an opportunity to answer the important question of the impact of SVR on clinical outcomes. If SVR with IFN did not affect but was rather a component of a good prognosis, in the DAA era with almost all treated patients achieving SVR, the association between SVR and improved favorable outcomes should diminish. Even patients who would not have achieved SVR with IFN-based therapy now achieve SVR reliably, despite risk factors for liver-related complications. If SVR does not affect prognosis, "IFN nonresponders" who now achieve SVR with DAAs would have a worse prognosis than individuals who achieved SVR with IFN.

A careful evaluation of outcomes with and without SVR among patients treated with IFN-based therapy and similar patients treated with DAAs should help clarify whether SVR alters prognosis, a key question to help guide the rational use of these expensive new antivirals. As such, outcomes after treatment were compared between patients treated with DAAs or IFN-based therapy who did and did not achieve SVR. Importantly, to ensure groups were comparable, the analysis was restricted to patients eligible for IFN therapy.

METHODS

Patients

All patients with chronic HCV infection who initiated treatment at the Toronto Centre for Liver Disease from June 2006 to December 2016 with known treatment outcome (SVR or non-SVR) were included. Follow-up data were acquired until December 2018. Patients had been treated with either IFN and ribavirin or an IFN-free DAA regimen. SVR was defined as undetectable HCV RNA at 24 weeks after IFN-based therapy and 12 weeks after DAA therapy [5–8]. Patients were excluded if they were coinfected with HIV, had HCC, or had received a liver transplant prior to the end of treatment.

Baseline data were collected on patients demographics, comorbidities, and start-of-treatment laboratory parameters (Supplementary Methods 1).

The tolerability of DAAs allows for their use in patients with advanced cirrhosis, whereas IFN-based therapy was contraindicated [20, 21]. Outcomes in all patients were included; however, to overcome the major confounder of liver disease severity, the analysis comparing outcomes in DAA- vs IFN-treated patients was restricted to IFN-eligible patients, which was defined using the inclusion criteria for the Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) trial, a phase IV clinical trial comparing pegylated IFN-α2a vs pegylated IFN-α2b [22]. This trial excluded patients with current or past hepatic decompensation (ascites, variceal hemorrhage, or hepatic encephalopathy), absolute neutrophil count of < 1500 cells/mm^3, a platelet count of < 80 000 k/μL, and hemoglobin < 12 g/dL (women) or < 13 g/dL (men). Patients were excluded if baseline IDEAL laboratory values were missing. Ethics approval was acquired through the Research Ethics Board at University Health Network.

Clinical Outcome Measures

The primary outcome was liver-related event-free survival. Patients had follow-up until a liver-related event occurred or a patient died. Patients not reaching an outcome were censored at the last visit date. Liver-related events were defined as hepatic decompensation and HCC. The definition of decompensation included the first episode of ascites, bleeding varices, or overt hepatic encephalopathy. The diagnosis of HCC, based on the American Association for the Study of Liver Diseases guidelines, was made by histopathological confirmation or 2 dynamic imaging techniques [23].

Statistical Analysis

Baseline characteristics were compared between patients receiving the different treatment regimens (IFN vs DAA), using the Mann-Whitney test for continuous nonparametric variables, the *t* test for continuous parametric variables, and the χ^2 test for categorical variables. Analyses were adjusted for patients with multiple treatments (Supplementary Methods 2). The Kaplan-Meier method was used to assess the cumulative incidence of clinical events during follow-up, and differences in categorical variables were assessed using the log-rank test. The crude incidence rate per 10 000 person-years (PY) for each treatment regimen was calculated for all IDEAL-eligible patients and for IDEAL-eligible patients with cirrhosis.

Inverse probability of treatment weighting (IPTW) was used to investigate whether SVR leads to a change in the prognosis of DAA-treated patients by applying risk factors associated with disease progression present in the IFN non-SVR population to the DAA-treated patients. A propensity model was built to predict non-SVR among IFN-treated patients, which included age, sex, ethnicity, presence of diabetes mellitus (DM), anti–hepatitis B core antigen (HBc) status, HCV genotype, cirrhosis, platelet count, neutrophil count, and hemoglobin. This model was then applied to patients treated with DAAs to identify patients with a "propensity to non-SVR" with IFN. IPTW was calculated using these scores and the stabilized weight was then applied to the DAA population. The 24-month event rate was then calculated for the IFN non-SVR population, the crude DAA population, and the weighted DAA population.

Cox proportional hazards regression was used to analyze the association between baseline risk factors, SVR, and disease progression. Multivariable models were constructed for liver-event-free survival using variables known to be related to outcome and those with a *P* value < .20 in univariable analysis in a stepwise backward selection approach.

Table 1. Baseline Characteristics

Characteristics	Overall			IDEAL-Eligible			IDEAL-Ineligible			IDEAL-Eligible vs IDEAL-Ineligible	
	IFN (n = 914)	DAA (n = 873)	*P* Value	IFN (n = 672)	DAA (n = 634)	*P* Value	IFN (n = 242)	DAA (n = 239)	*P* Value	IFN *P* Value	DAA *P* Value
Age, y, median (IQR)	51 (44–57)	59 (53–64)	< .001	50 (43–57)	59 (52–64)	< .001	53 (47–59)	60 (53–64)	< .001	< .001	.02
Male sex	567 (62)	543 (62)	.94	424 (63)	392 (62)	.64	143 (59)	151 (63)	.36	.27	.71
BMI, kg/m^2, median (IQR) (n = 1255)	27 (23–30)	27 (24–30)	.09	26 (23–30)	27 (24–30)	.05	27 (24–30)	27 (24–31)	.98	.23	.999
Diabetes mellitus	123 (14)	122 (14)	.75	84 (13)	68 (11)	.32	39 (16)	54 (23)	.07	.16	< .001
HBV anti-core positive	231 (25)	175 (20)	.008	157 (23)	123 (19)	.08	74 (31)	52 (22)	.03	.03	.44
History of alcohol use	124 (14)	153 (18)	.02	87 (13)	100 (16)	.15	37 (15)	53 (22)	.05	.36	.03
NAFLD	240 (26)	174 (20)	.002	184 (27)	123 (19)	.001	56 (23)	51 (21)	.64	.20	.52
Genotype HCV											
1	545 (60)	95 (80)	< .001	399 (59)	528 (83)	< .001	146 (60)	167 (70)	.19	.09	< .001
2	124 (14)	59 (7)		90 (13)	39 (6)		34 (14)	20 (8)			
3	207 (23)	87 (10)		159 (24)	51 (8)		48 (20)	36 (15)			
4	24 (3)	28 (3)		13 (2)	14 (2)		11 (5)	14 (6)			
5	1 (0.1)	1 (0.1)		11 (2)	2 (0.3)		1 (0.4)	1 (0.4)			
6	13 (1)	3 (0.3)		…	…		2 (0.8)	1 (0.4)			
Cirrhosis	265 (29)	366 (42)	< .001	140 (21)	190 (30)	< .001	125 (52)	176 (74)	< .001	< .001	< .001
Laboratory results, median (IQR)											
Platelets, × 10^9/L	182 (129–234)	179 (121–226)	.11	197 (159–243)	195 (152–238)	.25	110 (63–173)	89 (62–181)	.27	< .001	< .001
Hemoglobin, g/L	146 (134–156)	146 (133–158)	.26	149 (140–159)	151 (140–160)	.08	127 (115–139)	126 (114–140)	.84	< .001	< .001
Neutrophils, × 10^9/L	3.0 (2.2–3.9)	3.4 (2.6–4.4)	< .001	3.2 (2.5–4.1)	3.6 (2.8–4.6)	< .001	1.8 (1.2–2.8)	2.6 (1.8–3.7)	< .001	< .001	< .001
Albumin, g/L	41 (39–43)	41 (38–43)	.008	42 (40–44)	42 (40–44)	.29	38 (34–41)	36 (32–40)	.002	< .001	< .001
Total bilirubin, umol/L	11 (8–15)	12 (9–17)	.003	11 (8–14)	11 (8–15)	.16	14 (10–21)	17 (11–29)	< .001	< .001	< .001
SVR	454 (50)	840 (96)	< .001	352 (52)	617 (97)	< .001	102 (42)	223 (93)	< .001	.006	.006

Data are presented as no. (%) unless otherwise indicated.
Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; HBV, hepatitis B virus; IDEAL, Individualized Dosing Efficacy vs Flat Dosing to Access Optimal Pegylated Interferon Therapy; IFN, interferon; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; SVR, sustained virologic response.

To determine whether results from the first 24 months of follow-up could be extrapolated to longer follow-up, the probability of survival without a liver-related event for the first 24 months post-SVR was compared to the probability of survival without a liver-related event from 24 months up to 120 months of follow-up by using the hazard per year.

All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. SPSS version 24 (SPSS Inc) and RStudio version 1.0.153 software packages were used for analysis.

RESULTS

Patient Characteristics

The total number of treatments between June 2006 and June 2016 was 1 787 914 with IFN and 873 with DAAs. In total, 1306 (73%) patients were IDEAL-eligible, of whom 672 (52%) received IFN-based and 634 (49%) received DAA-based therapy. Of the 481 IDEAL-ineligible cases, 242 (50%) received IFN-based therapy and 239 (50%) were treated with DAAs. Baseline characteristics are shown in Table 1 according to treatment regimen and IDEAL eligibility. Overall, SVR was attained by 454 patients (50%) treated with IFN-based therapy, compared to 840 (96%) of the DAA-treated group ($P < .001$).

Focusing on the IDEAL-eligible patients, the median age was 50 (interquartile range [IQR], 43–57) years for IFN-based treatment and 59 (IQR, 52–64) years for DAAs ($P < .001$), and a similar proportion were male (63% vs 62%, respectively; $P = .64$). Cirrhosis was present in 140 (21%) patients in the IFN group, compared to 190 (30%) among DAA-treated patients ($P < .001$). SVR was attained in 352 (52%) patients who received IFN, compared to 617 (97%) of the patients treated with DAAs ($P < .001$). Median follow-up time for IDEAL-eligible cases was 17 months overall (IQR, 7–64 months) but differed markedly between

groups, with 61 (IQR, 16–109) months for the IFN group and 7 (IQR, 5–17) months for the DAA cohort. Median follow-up time for patients with cirrhosis was 26 (IQR, 15–53) months overall, but 64 (IQR, 26–96) months for those who received IFN and 20 (IQR, 7–29) months for those treated with DAAs.

IDEAL-Eligible Versus IDEAL-Ineligible Patients

To investigate whether IDEAL eligibility is a dependable approach to control for disease severity, IDEAL-eligible and IDEAL-ineligible patients were compared. Baseline characteristics differed significantly between patients categorized as IDEAL-eligible and IDEAL-ineligible as shown in Table 1. SVR rates were higher in IDEAL-eligible patients compared to IDEAL-ineligible, both for IFN (52% vs 42%) and DAAs (97% vs 93%). The 24-month event-free survival for patients who achieved SVR was 98% (95% confidence interval [CI], 23.8%–24.0%) for IDEAL-eligible patients and 82% (95% CI, 20.4%–22.0%) for IDEAL-ineligible patients (log-rank $P < .0001$), compared to 96% (95% CI, 23.2%–23.8%) in IDEAL-eligible and 63% (95% CI, 16.4%–19.3%) in IDEAL-ineligible patients who did not achieve SVR (log-rank $P < .0001$), respectively, highlighting the importance of considering IFN eligibility as a proxy for severity of liver disease when comparing patients treated in the IFN and DAA eras.

Occurrence of Complications

Focusing on events in IDEAL-eligible patients, the event-free survival at 10 years for all SVR patients was 93% compared to 74% for patients who did not achieve SVR (log-rank $P < .0001$; Figure 1). Truncated to 24 months, 21 events occurred, resulting in a 24-month event rate of 1.6%. Eight events occurred in the SVR group, compared to 13 in the non-SVR group, resulting in a 24-month event rate of 0.8% and 3.9%, respectively (log rank $P = .05$). Outcomes included 9 cases of decompensation (6 ascites, 2 variceal bleed, and 1 hepatic encephalopathy), 8 cases of HCC, 2 cases of liver-related mortality, and 2 instances of non-liver-related mortality (Table 2). All events occurred in patients with cirrhosis at baseline. Univariable analysis showed that baseline lower albumin, higher age, lower platelet count, higher total bilirubin, severe alcohol use, and DM were associated with a significantly increased risk. SVR was associated with a reduced risk of clinical outcome at 10 years (hazard ratio [HR], 0.34 [95% CI, .19–.59]; $P < .0001$), which remained significant (adjusted HR [aHR], 0.24 [95% CI, .14–.44]; $P < .0001$) after controlling for albumin ($P < .0001$), age ($P < .0001$), severe alcohol use ($P = .001$), DM ($P = .01$), and platelet count ($P = .05$).

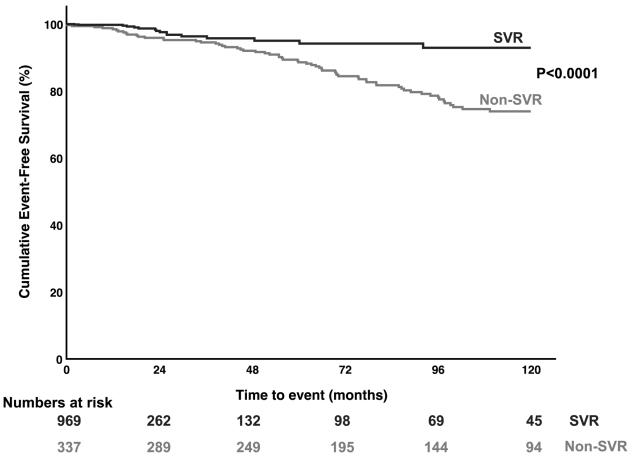

Figure 1. The 10-year event-free survival for IDEAL–eligible patients. Abbreviations: IDEAL, Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy; SVR, sustained virologic response.

DAA Versus IFN

To be able to compare the effects of SVR and non-SVR, the crude incidence rates of DAA and IFN were compared. Patients treated with DAAs were older, had a higher prevalence of cirrhosis, and had lower platelet counts, compared with IFN-treated patients (Table 1); however, the crude incidence of complications for IFN-treated patients, 17.0/10 000 PY (95% CI, 13.3–20.7), was higher than for those treated with DAAs (14.7/10.000 PY [95% CI, 6.0–23.3]). Restricted to patients with cirrhosis, the higher incidence of events in the IFN group (63.0/10 000 PY [95% CI, 47.0–78.9]) was more pronounced compared to DAA-treated patients (29.5/10.000 PY [95% CI, 12.1–47.0]).

In the SVR group, 6 events (1.0%) occurred in the DAA group and 2 (0.6%) in the IFN group (log-rank $P = .08$; Figure 2; Table 2). Similar to in the whole population, SVR in IDEAL-eligible patients was associated with a reduced event rate (HR, 0.42 [95% CI, .17–1.02]; $P = .06$). When adding the treatment regimen into the model, SVR remained significant (HR, 0.18 [95% CI, .05–.59]; $P = .005$). After adjusting for age ($P = .03$) and albumin ($P = .001$), SVR was associated with a reduced risk for a liver-related event (aHR, 0.22 [95% CI, .07–.70]; $P = .01$) and treatment with DAAs was not significantly associated with risk of liver-related events ($P = .25$) (Table 3).

Outcomes in IFN Non-SVR Population

To focus on the impact of increasing the SVR rate on the prognosis, keeping all else equal, the event rate in IFN non-SVR patients was compared to the event rate in a similar population of DAA-treated IFN-eligible patients (Supplementary Table 1). Among IDEAL-eligible patients who were IFN nonresponders, the 24-month event rate was 3.4%. The event rate at 24 months among IDEAL-eligible patients who received DAAs, of whom 97% achieved SVR, was 1.3% ($P = .02$ compared to IFN-nonresponders). After applying stabilized IPTW weights to the DAA population, the SVR rate remained at 97%; the event rate was 1.1% with 5 of 7 events in the SVR group ($P = .009$ compared to IFN non-SVR group), indicating a better-than-expected event-free survival in the DAA-treated patients.

Table 2. Liver-Related Events in IDEAL-Eligible Patients With Follow-up Truncated at 24 Months

Event	SVR			Non-SVR		
	DAA (n = 617)	IFN (n = 352)	Total (n = 969)	DAA (n = 17)	IFN (n = 320)	Total (n = 337)
Overall event rate	6 (1)	2 (0.6)	8 (0.8)	2 (11.8)	11 (3.4)	13 (3.9)
Decompensation	1 (0.2)	0 (0)	1 (0.1)	1 (5.9)	7 (2.2)	8 (2.4)
HCC	3 (0.5)	1 (0.3)	4 (0.4)	1 (5.9)	3 (0.9)	4 (1.2)
Death	2 (0.3)	1 (0.3)	3 (0.3)	0 (0)	1 (0.3)	1 (0.3)

Data are presented as no. (%).
Abbreviations: DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; IDEAL, Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy; IFN, interferon; SVR, sustained virologic response.

Follow-up Beyond 24 Months

To investigate the comparability of the first 2 years of follow-up to a longer follow-up time, the hazard for an event at each year was used. The average hazard for an event in the first 2 years in patients that attained SVR was 4.0×10^{-4} for IFN, which was similar to the average hazard from years 2 to 10 (4.6×10^{-4}) (Supplementary Figures 1 and 2).

DISCUSSION

Understanding whether SVR is a meaningful clinically relevant surrogate endpoint or merely a component of a favorable natural history has important implications for HCV policy. In a large cohort of patients treated with IFN- or DAA-based antiviral therapy, we have shown that SVR is much more commonly achieved with DAAs and confers a similar clinical benefit as in those treated with IFN when evaluating a population with similar disease severity.

The significant differences in event rates between DAA- and IFN-treated patients in the IDEAL-ineligible category highlight the importance of controlling for disease severity when comparing these treatment regimens. DAAs can be used in patients with very advanced or even decompensated cirrhosis, a population that may still have a high event rate despite viral clearance [24–27].

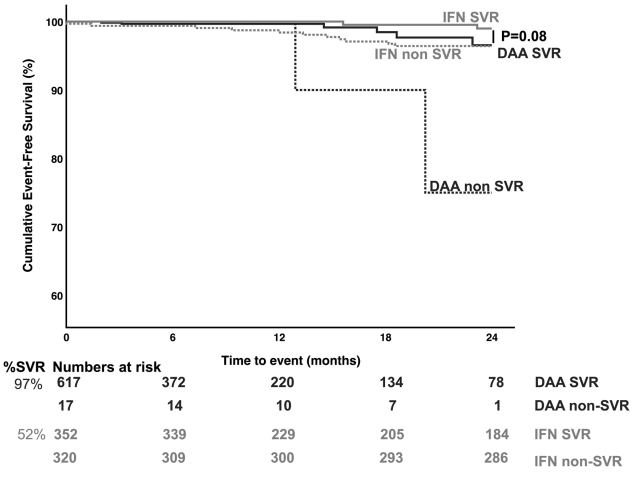

Figure 2. The 24-month event-free survival for IDEAL–eligible patients comparing direct-acting antivirals and interferon.
Abbreviations: DAA, direct-acting antiviral; IDEAL, Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy; IFN, interferon; SVR, sustained virologic response.

Although there are many studies suggesting a clinical benefit of SVR, the inherent biases of comparing patients who achieve SVR to those who do not or to those who achieve SVR to untreated patients are difficult to overcome [2, 11–14, 28]. In the IFN era, factors associated with disease progression were also associated with nonresponse to therapy, making it conceivable that those who achieved SVR were simply the patients who already had a favorable natural history. Patients who did not receive therapy were often those with advanced liver disease or significant comorbidities. The landscape has changed dramatically with the introduction of DAAs. Almost all patients are eligible for treatment, and almost all those treated achieve SVR. If SVR had no effect on long-term outcome, the rate of posttreatment events in the DAA era should increase due to treatment of older patients and those with more advanced disease. Indeed, the event rate in those with SVR is higher in patients treated with DAAs than those treated with IFN. However, if the analysis is restricted to those eligible for IFN, this difference disappears.

Even among IDEAL-eligible patients, those in the DAA group were older and had more advanced disease than those treated with IFN. However, the DAA group showed a reduced overall event rate compared to IFN. The major factor associated with improved outcome in the DAA-treated group was the much higher probability of SVR. To isolate the effect of SVR, the outcomes in patients expected to be nonresponders to IFN but treated with DAAS were evaluated. Notably, the event rate in the weighted DAA population was even lower than in the crude DAA population. More importantly, the event rate in those treated with DAAs who would have been expected to fail IFN-based therapy was lower than in true IFN nonresponders, clearly demonstrating that SVR changed the prognosis for this group of patients. Short of a randomized trial, this type of analysis is likely the best evidence possible to confirm the utility of SVR. These findings provide strong evidence for the relevance of SVR as an important surrogate endpoint conferring a lower risk of clinical outcomes. The findings are similar to the use of surrogates in HIV. Suppression of HIV viral load and improvement

Table 3. Cox Regression Analysis for Event-Free Survival Truncated at 24 Months

	Univariate Analysis			Multivariate Analysis		
Variable	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value
SVR	0.42	(.17–1.02)	.06	0.21	(.06–.71)	.01
DAA treatment	0.67	(.27–1.65)	.38	1.86	(.53–6.55)	.34
Age	1.07	(1.02–1.12)	.003	1.06	(1.01–1.12)	.03
Male sex	1.06	(.44–2.56)	.90		…	
Body mass index	1.05	(.98–1.13)	.16		…	
Diabetes mellitus	1.89	(.69–5.17)	.21		…	
History of severe alcohol use	1.91	(.70–5.21)	.21		…	
Laboratory data						
Platelet count per 10×10^9	0.99	(.98–1.00)	.005		…	
Albumin level, g/L	0.79	(.70–.88)	< .0001	0.87	(.76–.99)	.03
Total bilirubin, mg/dL	1.08	(1.05–1.11)	< .0001	1.05	(1.01–1.09)	.01
Anti-HBc positivity	0.60	(.18–2.04)	.42		…	

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; anti-HBc, anti–hepatitis B core antigen; HR, hazard ratio; SVR, sustained virologic response.

in $CD4^+$ T-cell count were initially used as endpoints for clinical trials, similar to SVR, but were later shown to predict long-term clinical improvement and as such became accepted as meaningful clinical endpoints [29]. Similarly, SVR should not be accepted as a meaningful clinical endpoint in HCV.

Notably, all posttreatment events occurred in patients with cirrhosis, highlighting the importance of treating patients prior to the development of advanced liver disease. Even in those with cirrhosis, SVR is associated with a reduced risk of events. Treatment of patients with early disease prevents progression to cirrhosis, thus markedly reducing if not eliminating the risk of long-term complications, as well as avoiding the need for prolonged follow-up [30–32].

This study has important limitations—most importantly, the short follow-up period for DAA-treated patients, as DAAs have only been widely available since 2015. However, our results show that even with a short follow-up, the difference between SVR and non-SVR is clear. In the IFN-era the rate of events in the first 24 months of follow-up after SVR was predictive of the rate with longer follow-up, giving us confidence that the early data with DAAs will also be reflective of future events [33]. As with all retrospective cohorts, there were missing data and patients lost to follow-up. However, the amount of missing data was limited, and follow-up was most complete in patients with cirrhosis. After applying the propensity scores for IFN nonresponse to the DAA population, the event rate was lower than that of the crude DAA population. This suggests that even when controlling for disease severity by using criteria for IFN eligibility, DAA-treated patients are still sicker and have a higher risk for disease progression. However, as the event rate in the DAA population remained lower than in the IFN nonresponder population, the conclusion that SVR changes prognosis holds.

In conclusion, our study shows that SVR is a relevant endpoint leading to improved clinical outcomes. Even among IFN-eligible patients, those treated with DAAs were enriched for factors associated with worse outcome, yet they had a lower event rate than those treated with IFN due to the markedly higher rate of SVR. These data clearly demonstrate that SVR is not part of a good prognosis but rather a determinant of an improved prognosis, and thus a clinically relevant endpoint.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Study concept and design, acquisition of data, and critical revision of the manuscript for important intellectual content: All authors. Analysis and interpretation of data: L. A. P. K., B. E. H., J. J. F. Drafting of the manuscript: L. A. P. K., B. E. H., J. J. F. Statistical analysis: L. A. P. K., B. E. H., J. J. F. Authors L. A. P. K., B. E. H., and J. J. F. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analyses.

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