Induction with T cell-depleting antibodies was used in 83% of recipients, and 76% of patients received tacrolimus, mycophenolate, and prednisone for maintenance immunosuppression. As ethnicity, duration of dialysis prior to transplantation, donor source, and immunosuppression may all impact outcomes and potentially modify the effects of diabetes, the results may be less applicable to programs with largely non-Caucasian populations, a higher proportion of deceased donors, longer waiting times, or different immunosuppressive protocols.

The data presented clearly demonstrate that excellent transplant outcomes are achievable for a significant proportion of patients with diabetes and ESKD, and thus diabetes should not be viewed as a contraindication to kidney transplantation. Should we then, on the basis of these data, liberalize access to transplantation for diabetic patients with ESKD? The authors, quite reasonably, suggest we should 'give consideration' to this. In doing so, we must consider more than just crude patient survival. Indeed, modeling studies that have examined incremental costs and benefits of transplantation vs. dialysis demonstrate that wait-listing and giving transplants to patients with diabetes is highly cost-effective and prolongs life, relative to non-listing.[7] The impacts of transplantation on recipient quality of life, carer and family life, cost of care to society, and opportunity cost for those not given transplants all warrant close consideration. Substantial changes to wait-listing policy and organ allocation require modeling of data obtained from registries and cohort studies, informed by ethical and societal considerations, to determine the outcomes of those given and those not given transplants. To this end, the data provided by Keddis *et al.*[5] make an important contribution.

DISCLOSURE
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Novel evidence on hepatitis C virus–associated glomerular disease

Fabrizio Fabrizi[1,2], Piergiorgio Messa[1] and Paul Martin[2]

A large spectrum of renal pathology is associated with hepatitis C virus (HCV). According to novel evidence, occult HCV infection (HCV-RNA in peripheral blood mononuclear cells or in serum after ultracentrifugation) could be involved in the pathogenesis of glomerular nephropathy among patients negative for conventional markers of HCV. Additional studies with appropriate size and technology are in progress to confirm the relationship between occult HCV and glomerular disease, which has multiple implications from the clinical standpoint.

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Hepatitis C virus (HCV) has an estimated prevalence of 3% worldwide (around 170 million infected individuals all over the world) and remains a major global health burden. The long-term hepatic impact of HCV infection includes chronic hepatitis, and cirrhosis, with or without hepatocellular carcinoma. Several extrahepatic manifestations have been associated with HCV infection, including hematologic, dermatologic, autoimmune, and kidney diseases. There is increasing evidence of an association between HCV infection and glomerular disease both in native kidneys and after kidney (or liver) transplantation. The most common type of HCV-related glomerulonephritis is type I membranoproliferative glomerulonephritis, usually in the context of type II cryoglobulinemia. HCV-infected patients show less common glomerular diseases including membranoproliferative glomerulonephritis without cryoglobulinemia, membranous nephropathy, focal segmental

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Table 1 | Occult hepatitis C virus infection in chronic kidney disease and other patient groups

Authors	Prevalence	Study group	Reference year
Barril *et al.*[12]	45% (49/109)	Chronic hemodialysis	2008
Nicot *et al.*[13]	0% (0/26)	Renal transplantation	2010
De Marco *et al.*[14]	1.27% (4/314)	Infective liver disease-free patients	2009
Zaghloul & El-Sherbiny[15]	10% ((4/40)	Chronic liver disease	2010
Idrees *et al.*[16]	74% (23/31)	Cryptogenic liver disease	2011
Bokharaei-Salim *et al.*[17]	8.9% (4/45)	Cryptogenic chronic liver disease	2011
Farahani *et al.*[18]	1.9% (2/104)	Lymphoproliferative disorders	2013
Keyvani *et al.*[19]	8.9% (4/45)	Cryptogenic cirrhosis	2013

sclerosis, mesangial glomerulonephritis, and fibrillary and immunotactoid glomerulopathies. Anecdotal information has been reported on HCV-associated IgA nephropathy, and cryoglobulinemic thrombotic microangiopathy. In addition to glomerular disease, tubulointerstitial injury has been also observed in association with HCV infection.

The most important survey on the epidemiology of HCV-associated glomerular disease has been conducted by El-Serag *et al.*[1] They carried out a hospital-based case–control study that enrolled all cases of HCV-infected patients hospitalized during the 1990s ($n = 34{,}204$) and randomly chosen control individuals without HCV ($n = 136{,}816$) matched with cases on the year of admission. As expected, cryoglobulinemia was more common in cases than controls (0.57 vs. 0.05%, $P < 0.0001$), and a greater prevalence of membranoproliferative glomerulonephritis (0.36 vs. 0.05%) but not membranous nephropathy (0.33 vs. 0.19%) was observed in HCV-infected individuals. A recent meta-analysis of clinical studies (four clinical studies with 81,286 unique individuals) demonstrated that HCV-seropositive status was an independent and significant risk factor for proteinuria in the general population, with a summary estimate for adjusted relative risk of 1.47 (95% confidence interval (CI), 1.12–1.94; $P = 0.006$). Significant heterogeneity occurred (proportion of total variance due to between-studies variance (Ri) = 0.82; P value by Q-test, <0.001).[2] Proteinuria clusters with the metabolic syndrome, and surveys have reported a relationship between proteinuria and individual components of the metabolic syndrome (insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and arterial hypertension). Because patients with HCV are known to have higher prevalence of components of the metabolic syndrome, it has been hypothesized that individuals with HCV may have high frequency of proteinuria. The persistence of the relationship between HCV and proteinuria after correction for several confounding parameters including metabolic syndrome elements suggests the occurrence of HCV-associated cryoglobulinemic or intrinsic renal disease.

The main clinical manifestations of HCV-associated glomerular disease are the presence of proteinuria and microscopic hematuria with or without impaired kidney function. It has been recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) HCV guidelines that patients infected with HCV be tested at least annually for proteinuria, hematuria, and estimated glomerular filtration rate (eGFR).[3] HCV-infected patients with clinical evidence of glomerulonephritis should undergo kidney biopsy, and the outcome of HCV-associated glomerulonephritis is improved by early diagnosis and therapy. The routine laboratory diagnosis of HCV-related glomerulonephritis is based on the presence of conventional markers of HCV infection such as anti-HCV antibody and HCV viremia (HCV-RNA). The disappearance of proteinuria after interferon therapy with clearance of HCV-RNA from serum gives emphasis to the pathogenetic activity of HCV in this glomerular disease.[3]

Castillo *et al.*[4] (this issue) have hypothesized the role of occult HCV infection in the development of HCV-associated glomerular disease, occult HCV being detectable viral RNA in peripheral blood mononuclear cells or in serum after ultracentrifugation in anti-HCV-negative patients without serum HCV-RNA. In their prospective study on anti-HCV-negative/HCV-RNA-negative patients, occult HCV was more common in immune-mediated than hereditary glomerular disease, 39% (34/87) vs. 3.8% (1/26), $P = 0.015$.[4] Occult HCV has been documented in various populations, including hemodialysis patients, patients with cryptogenic hepatitis and liver cirrhosis, hepatocellular carcinoma, lymphoproliferative disorders, and healthy individuals without evidence of liver disease (Table 1).[5] As shown in Table 1, the frequency of occult HCV infection is very heterogeneous, and differences in the methods by which diagnosis of occult HCV is made are probably an important reason. The role played by occult HCV infection in the pathogenesis of HCV-associated glomerular disease is in agreement with some pieces of evidence; as an example, interferon-based therapy has given benefit in some cases of HCV-negative cryoglobulinemic glomerulonephritis. HCV antigens or particles have been found in the kidney tissue of patients with HCV-negative glomerulonephritis. If confirmed, occult HCV infection could be the underlying cause of glomerular disease in some patients with negative serologic viral markers, and detection of occult HCV might be the rationale for antiviral therapy in anti-HCV-negative glomerular nephropathy.

The mechanisms of HCV-related renal disease are uncertain, but research suggests that HCV-associated glomerular injury results from deposition of circulating immune complexes containing HCV proteins, anti-HCV antibody, and rheumatoid factor IgM with anti-IgG activity. Viral antigens have been found by immunochemistry, and by *in situ* hybridization. Some authors have used laser microdissection to detect HCV-RNA genomic sequences of HCV core protein in glomeruli and tubules of patients with HCV-associated glomerular disease. Recently, an elevation of toll-like receptor 3 (TLR3) mRNA expression in glomeruli, particularly mesangial cells, of patients with

HCV-induced glomerulonephritis has been seen, associated with an increased activity of some proinflammatory cytokines. A greater TLR3 expression was observed in peripheral mononuclear cells of patients with HCV-positive glomerulonephritis ($n=46$) compared with HCV-negative patients ($n=32$) or healthy individuals ($n=20$) ($P<0.0001$).[6] Another possible mechanism underlying HCV-related glomerular disease is nonimmunologically mediated—many studies have shown a link between anti-HCV-positive serologic status and increased insulin resistance and hyperinsulinemia. Insulin resistance and hyperinsulinemia can give excess intrarenal production of insulin-like growth factor-1 and transforming growth factor-β, thus triggering proliferation of renal cells and upregulation of the expression of angiotensin II type 1 receptors in mesangial cells, which in turn enhances oxidative activity at the kidney level.

The association between HCV infection and the development or progression of kidney disease is more controversial. Although the prevalence of HCV is much higher among patients with end-stage renal disease (ESRD) than in the general population, it is unknown whether this reflects an increased risk of viral exposure, a greater incidence and progression of kidney disease in individuals with HCV, or both. The adverse impact of HCV infection on the risk of developing ESRD has been observed in diabetic patients, in individuals with HIV and HCV coinfection, and in cirrhotics who completed interferon therapy. Crook *et al.*[7] identified 312 pre-ESRD patients with diabetes mellitus (24 being anti-HCV seropositive); Cox proportional hazard analysis reported that anti-HCV-seropositive status was a significant and independent predictor of ESRD after correction for multiple independent parameters 3.49 (95% CI, 1.27–9.57; $P<0.015$). In the Women's Interagency HIV Study ($n=2684$ HIV-infected women), 180 women with HIV and HCV coinfection and chronic kidney disease at baseline (eGFR <60 ml/min per 1.73 m^2) had a greater fully adjusted decline in eGFR over time (–5.2% change per year; 95% CI, –3.2 to –7.2; $P<0.001$) than HCV-seronegative women.[8] In the survey of Arase *et al.*, 650 patients with HCV-related cirrhosis were followed up for a mean period of 6.5 years after completing interferon therapy. Non-clearance of HCV was linked to the development of chronic kidney disease (eGFR <60 ml/min per 1.73 m^2), adjusted hazard ratio 2.67 (95% CI, 1.34–5.32; $P=0.005$).[9]

Additional data support a detrimental role of HCV in the development of ESRD. Satapathy *et al.* retrospectively evaluated 552 patients with serum positive for antibody against HCV and found that baseline high viral HCV load (HCV-RNA $>700{,}000$ copies/ml) was an independent predictor of chronic kidney disease (adjusted odds ratio, 2.45; 95% CI, 1.21–4.98; $P=0.01$).[10] In a longitudinal study (4 years) on 111 patients with biopsy-proven glomerulonephritis (21% being HCV positive), Noureddine *et al.* found that HCV-seropositive patients had a greater risk of progression to ESRD than HCV-negative individuals, according to Cox regression analysis (adjusted hazard ratio, 0.37; 95% CI, 0.19–0.76; $P<0.05$), but this became non-significant after adjustment for mean arterial pressure and hemoglobin.[11] In contrast, no relationship between positive anti-HCV serologic status and reduced GFR (<60 ml/min per 1.73 m^2) in the general population (adjusted relative risk, 1.12; 95% CI, 0.91–1.38; $P=0.28$) was found in our pooled analysis of observational studies.[2] We have updated our systematic review of the published medical literature; only longitudinal studies ($n=7$; 710,024 unique individuals) were retrieved. Pooling of study results demonstrated a relationship between HCV seropositivity and incidence of reduced eGFR (adjusted relative risk, 1.70; 95% CI, 1.20–2.39; $P=0.002$); substantial heterogeneity (proportion of total variance due to between-studies variance (Ri) $=0.98$; P value by Q-test, <0.00001) without publication bias was detected. The heterogeneity among studies could be related to occult HCV, in addition to differences in the clinical and demographic characteristics of the study populations, as well as the methods for measuring renal impairment.

In conclusion, preliminary evidence suggests a high frequency of occult HCV infection in patients with glomerular disease who are anti-HCV antibody negative without serum HCV-RNA. Further studies are needed to clarify the epidemiology and significance of occult HCV infection in patients with glomerular disease. Standardization of methods for detection of occult HCV should be considered in future studies on this subject.

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Pleiotropic effects of angiotensin II blockers in hemodialysis patients: myth or reality?

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Mechanistic studies suggest that angiotensin II receptor blockers (ARBs) may have pleiotropic effects on the cardiovascular system in hemodialysis patients. A new randomized trial by Peters *et al.* failed to show a benefit of irbesartan on biomarkers of arterial stiffness, left ventricular mass, and autonomic nerve function. Their findings suggest that, like in the general population and other disease states, in hemodialysis patients the type of antihypertensive drug is unlikely to be of major clinical relevance.

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The proportion of patients who die of cardiovascular disease in stage 5 chronic kidney disease on dialysis (5D-CKD) is almost identical to that observed in the general population.[1] However, due to the extremely high mortality rate in 5D-CKD (at least ten times higher than that in the background general population), in absolute terms the number of deaths attributable to cardiovascular causes in these patients is enormous. In contrast with studies based on predialysis blood pressure (BP), studies based on 24-hour ambulatory BP monitoring in hemodialysis patients with no cardiovascular involvement or just moderate cardiovascular involvement documented that 24-hour average systolic BP[2] and nocturnal systolic BP[3] are quite strong predictors of death, emphasizing the relevance of hypertension in the high risk for cardiovascular death in 5D-CKD. Optimization of body fluid balance by long and/or frequent hemodialysis is the fundamental intervention to control hypertension. However, this intervention fails to normalize BP in about 40% of cases. In the clinical scenario, the hard reality is that antihypertensive medications are used in the vast majority of patients. In the face of the widespread use of these drugs, the number of randomized trials based on meaningful clinical end points in hypertensive hemodialysis patients is very meager indeed. A meta-analysis by Heerspink *et al.*[4] in 2009 was based on just eight trials, including a very small study in patients on peritoneal dialysis, two studies in patients with left ventricular (LV) systolic dysfunction or overt cardiac failure and normal or low BP, and a trial that enrolled patients with LV hypertrophy, independent of BP. Subsequently, the Olmesartan Clinical Trial in Okinawan Patients Under OKIDS (OCTOPUS) trial in hypertensive 5D-CKD patients was published in 2013[5] and the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial in 2014.[6] In all, only five drug trials based on clinical end points and specifically looking at the treatment of hypertension in hemodialysis patients have been performed. Three of these trials, all performed in Japan, tested angiotensin II receptor blockers (ARBs) (Figure 1). In two of these trials the risk of cardiovascular events was remarkably lower (–47% and –71%) in patients treated with ARBs, while in the third trial, the largest performed so far, no such benefit was observed. A meta-analytical estimate of the risk reduction by ARBs shows a non-significant ($P = 0.10$) 42% risk reduction, which seems to be completely independent of BP (Figure 1). Thus the apparent beneficial effect of ARBs in 5D-CKD apparently rests on the pleiotropic effects of these drugs, a hypothesis supported by the observation that, independently of BP, telmisartan reduced the death rate in hemodialysis patients with chronic heart failure (New

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