Irbesartan delays progression of nephropathy as measured by estimated glomerular filtration rate: post hoc analysis of the Irbesartan Diabetic Nephropathy Trial

Marc Evans1, Stephen C. Bain2, Simon Hogan3 and Rudy W. Bilous4,5; on behalf of the Collaborative Study Group participants*

1University Hospital Llandough, Cardiff, UK, 2Institute of Life Science, Swansea University and ABM University Health Board, Swansea, UK, 3Sanofi-aventis, Surrey, UK, 4Newcastle University, Newcastle, UK and 5James Cook University Hospital, Middlesbrough, UK

Correspondence and offprint requests to: Rudy W. Bilous; E-mail: rudy.bilous@stees.nhs.uk

*The participants in the Collaborative Study Group are listed in the Supplementary material.

Abstract

Background. The Irbesartan Diabetic Nephropathy Trial (IDNT) demonstrated that irbesartan significantly slowed established Type 2 diabetic nephropathy progression. Estimated glomerular filtration rate (eGFR), now widely used to monitor chronic kidney disease (CKD) progression, was not previously examined in IDNT. This post hoc analysis aimed to confirm IDNT results using eGFR as principal outcome measure.

Methods. Mean change in eGFR from baseline (ΔeGFR) was analysed using linear mixed-effects models over time and analysis of covariance at end of study on an intention-to-treat basis. Potential treatment response moderators and/or mediators assessed were CKD stage, blood pressure (BP) and proteinuria.

Results. Irbesartan significantly slowed the rate of ΔeGFR decline from 6 to 21 months (P = 0.0048) and 24 to 48 months (P < 0.0001) versus amlodipine and placebo, despite a faster decline in the first month. The longer patients remained on irbesartan the greater the benefit (model-derived estimates for 6–21 and 24–48 month periods were /C0 0.3354 and /C0 0.1947 mL/min/1.73m2/month, respectively). Irbesartan slowed the rate of ΔeGFR decline irrespective of baseline CKD stage, BP or proteinuria level. Irbesartan produced rapid and sustained proteinuria reductions, which only partially mediated treatment response. Irbesartan increased serum potassium, but levels stabilized from 6 to 48 months.

Conclusions. In patients with established Type 2 diabetic nephropathy and CKD Stages 1–5, irbesartan safely and significantly slowed the rate of ΔeGFR decline (−2.34 mL/min/1.73m2/year) compared to amlodipine (−3.76 mL/min/1.73m2/year) and placebo (−3.52 mL/min/1.73m2/year). This rate of decline was slower with longer duration of irbesartan treatment and only partly explained by observed reductions in BP and proteinuria.

Keywords: chronic kidney disease; diabetes; diabetic nephropathy; glomerular filtration rate; irbesartan

Introduction

In 2010, the estimated prevalence of diabetes mellitus in adults was 285 million worldwide and is expected to rise to 439 million by 2030 [1, 2]. Diabetes, followed by hypertension, is the leading cause of end-stage renal disease (ESRD) in Europe [3] and the USA [4] and is associated with high cardiovascular morbidity and mortality [4].

In Europe, diabetes-related ESRD incidence increased by 6% annually during the period 1997–2000 and 2.4% from 2000 to 2006 [5]. In the USA, incidence increased from 1990 to 1996, but in 1996–2006, it decreased by 3.9% annually [6]. The reasons are uncertain but may include earlier detection and treatment of kidney disease and improved management of ESRD risk factors, particularly glycaemia and hypertension [6], to recommended targets [7, 8]. Use of renin–angiotensin–aldosterone system (RAAS) inhibitors in patients with Type 2 diabetes mellitus and microalbuminuria is renoprotective [9] and ~77% of chronic kidney disease (CKD) patients with diabetes in the USA receive such agents [4]. However, physicians are hesitant to administer RAAS inhibitors to patients with CKD, particularly at later stages, because of concerns about acute worsening of renal function and/or hyperkalaemia [10, 11]. Indeed, US data show that the current use of such agents decreases as patients progress towards ESRD [4].

Recent clinical trials have shown that the angiotensin II receptor blockers (ARBs) irbesartan [12] and losartan [13] slow the progression of established diabetic nephropathy. The Phase III Irbesartan Diabetic Nephropathy Trial (IDNT) demonstrated that irbesartan significantly slowed progression of established Type 2 diabetic nephropathy compared to placebo and amlodipine [12].
Since the primary IDNT results were published, guidelines now recommend that estimated glomerular filtration rate (eGFR) is used as a preferred measure of renal function changes [7, 8, 14, 15]. CKD has been categorized into five stages based upon eGFR [8].

IDNT did not report eGFR. Therefore, the objectives of this study were (i) to perform post hoc analyses of IDNT data using eGFR to assess progression of nephropathy in Type 2 diabetes, hypothesizing that the rate of eGFR decline will differ between the three treatment groups and (ii) to determine whether results of IDNT were confirmed when using eGFR as the principal outcome measure.

Materials and methods

IDNT design

This has been described previously [12, 16, 17]. Patient inclusion criteria were age 30–70 years, hypertension [>135 mmHg seated systolic blood pressure (SBP), >85 mmHg seated diastolic blood pressure (DBP) or documented anti-hypertensive treatment], plus Type 2 diabetes with nephropathy (proteinuria >900 mg/24 h and serum creatinine 1.0–3.0 mg/dL for women and 1.2–3.0 mg/dL for men). Any ARBs, angiotensin-converting enzyme inhibitors and calcium channel blockers were stopped for at least 10 days prior to the study screening; during this time, BP was controlled using other agents.

Eligible patients were randomized to receive irbesartan (75–300 mg/ day), amlodipine (2.5–10 mg/day) or placebo. The target BP for all participants was SBP ≤135 mmHg or 10 mmHg lower than at screening if >145 mmHg, plus DBP ≤85 mmHg.

The following parameters were measured at baseline and every 3 months: survival, ESRD, serum creatinine and potassium and BP. Serum creatinine, potassium and BP were also measured after 1, 2 and 4 weeks and after 2 months. Twenty-four-hour urinary protein excretion was measured at baseline, 2 and 3 months, and then once every 6 months.

The primary end point was doubling of serum creatinine from baseline. ESRD (initiation of dialysis, renal transplantation or serum creatinine ≥6.0 mg/dL or death) [12].

Post hoc analyses statistical methods

Definitions. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate eGFR (mL/min/1.73m2) = 186 × (serum creatinine [mg/dL])−1.154 × (Age)−0.203 × (0.742 if female) × (1.210 if black). All recruited patients had CKD by definition (all were proteinuric). CKD stages were established from eGFR according to the National Collaborating Centre for Chronic Conditions criteria [8]. Stage 1: kidney damage with eGFR ≥90; Stage 2: kidney damage with eGFR 60–89; Stage 3: eGFR 30–59; Stage 4: eGFR 15–29 and Stage 5: kidney failure with eGFR ≤15 or receiving dialysis.

Analysis of treatment effects on change in eGFR over time. Mean change in eGFR from baseline (ΔeGFR) with treatment was analysed using linear mixed-effects models employing S-Plus Professional v6.1 Statistical Software (Insightful Corp.). Fixed effects included time and treatment, with random effects for patient and time. Quadratic and cubic polynomial time terms accounted for non-linearity of treatment effect. irbesartan was compared with placebo as reference category generated multiple slope estimates using placebo and amlodipine groups as a combined reference category. Transitions between statistically insignificant and significant slopes determined relevant points of divergence. Overall rates of change in ΔeGFR for the identified transition periods were then generated from the fitted model predictions.

Moderators and mediators of treatment effects on ΔeGFR. The influence of baseline CKD stage, blood pressure (BP) parameters, change in BP parameters, baseline proteinuria and change in proteinuria as potential moderators and mediators of treatment response was investigated according to the general statistical principles outlined by Kraemer et al. [18].

BP and ΔeGFR. Baseline seated DBP and seated SBP were entered into mixed-effects models with or without baseline BP-by-treatment interaction terms to identify independent and moderating influences on ΔeGFR treatment response.

Change from baseline DBP (∆DBP) or SBP (∆SBP) was entered into mixed-effects models as covariates with associated main effect, two-way and three-way interaction terms, while controlling for baseline DBP or SBP, to identify independent and mediating influences on ΔeGFR treatment response. Centred ∆DBP or ∆SBP variables compared interaction terms with reference to individuals with average changes in BP as most patients showed falls in BP.

Best-fitting models were identified by stepwise omission of non-significant terms and comparing the model fit parameters Akaike information criterion, Bayesian information criterion and change in log-likelihood ratio [19].

Proteinuria and ΔeGFR. The potential influence of baseline proteinuria and treatment-induced changes in proteinuria from baseline (ΔProt) on ΔeGFR was analysed similarly to the BP moderator/mediator analysis. Although raw proteinuria measurement distribution was positively skewed, ΔProt was normally distributed. ΔProt was therefore entered into mixed-effects analyses untransformed, but baseline proteinuria was log transformed prior to analysis. Using uncentred, ΔProt was considered to be most meaningful as patients showed both increases and decreases from baseline. Because the first non-baseline proteinuria measurement was at 2 months, intercept terms refer to initial treatment effects at 2 months and not at 1 week as for eGFR, BP and potassium analyses.

In the event of full or partial mediation over time, mean differences in ΔeGFR between patients classified by proteinuria increase from baseline versus proteinuria decrease at EOS for each treatment group was analysed using LOCF ANCOVA with baseline eGFR as covariate.

Changes in serum potassium with treatment. Mean change in serum potassium from baseline (ΔK+) with treatment was examined using mixed-effects models.

Results

Baseline characteristics and patient disposition

The baseline characteristics of the study population have been described in detail elsewhere [12, 17], but a summary is provided in Table 1. There were no significant differences in baseline eGFR between treatment groups.

Treatment effects on ΔeGFR

Irbesartan significantly slowed the rate of decline in ΔeGFR relative to placebo and amlodipine treatment as demonstrated by positive changes in slope compared with placebo and amlodipine. However, the intercept value suggested that at 1 week, irbesartan initially decreased ΔeGFR versus placebo (Figure 1 and Supplementary Table 1).

Using the LOCF method, ANCOVA confirmed that the effect of treatment was significant (d.f. = 2; $F = 7.755; P = 0.0004$) and that ΔeGFR deterioration at EOS was significantly less in patients treated with irbesartan than with placebo or amlodipine (Supplementary Table 1).
Analysis of slopes at each time point showed transitions from significant to insignificant values at 3 months and from insignificant to significant values at 21 months. Analysis of slopes at 1 week to 3 months, 6–21 months and 24–48 months confirmed that irbesartan initially increased the rate of ΔeGFR deterioration compared with placebo and

Table 1. Baseline patient characteristics and disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group (N = 569)</th>
<th>Amlodipine group (N = 567)</th>
<th>Irbesartan group (N = 579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>58.3 ± 8.2</td>
<td>59.1 ± 7.9</td>
<td>59.3 ± 7.1</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>403 (71)</td>
<td>359 (63)</td>
<td>378 (65)</td>
</tr>
<tr>
<td>Race or ethnic group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>415 (73)</td>
<td>389 (69)</td>
<td>438 (76)</td>
</tr>
<tr>
<td>Black</td>
<td>78 (14)</td>
<td>87 (15)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>26 (5)</td>
<td>29 (5)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>27 (5)</td>
<td>34 (6)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (4)</td>
<td>28 (5)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean ± SD</td>
<td>30.5 ± 5.9</td>
<td>30.9 ± 5.9</td>
<td>31.0 ± 5.6</td>
</tr>
<tr>
<td>BP (mmHg), mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>158 ± 20</td>
<td>159 ± 19</td>
<td>160 ± 20</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87 ± 11</td>
<td>87 ± 11</td>
<td>87 ± 11</td>
</tr>
<tr>
<td>Insulin use at entry, n (%)</td>
<td>335 (59)</td>
<td>327 (58)</td>
<td>329 (57)</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>164 (29)</td>
<td>171 (30)</td>
<td>158 (27)</td>
</tr>
<tr>
<td>Retinopathy, n (%)</td>
<td>380 (67)</td>
<td>362 (64)</td>
<td>401 (69)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL), mean ± SD</td>
<td>1.69 ± 0.57</td>
<td>1.65 ± 0.61</td>
<td>1.67 ± 0.53</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²), mean ± SD</td>
<td>47.7 ± 18.4</td>
<td>47.8 ± 17.6</td>
<td>46.4 ± 16.9</td>
</tr>
<tr>
<td>Serum potassium (mmol/L), mean ± SD</td>
<td>4.6 ± 0.49</td>
<td>4.6 ± 0.46</td>
<td>4.6 ± 0.52</td>
</tr>
<tr>
<td>Urinary protein excretion (g/24 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.8–5.2</td>
<td>1.6–5.2</td>
<td>1.6–5.4</td>
</tr>
<tr>
<td>Glycosylated haemoglobin (%)</td>
<td>8.2 ± 1.7</td>
<td>8.2 ± 1.7</td>
<td>8.1 ± 1.7</td>
</tr>
<tr>
<td>Never received study medication, n (%)</td>
<td>6 (1.1)</td>
<td>8 (1.4)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Lost to follow-up, n (%)</td>
<td>4 (0.7)</td>
<td>2 (0.4)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Duration of follow-up (months), mean</td>
<td>30.3</td>
<td>30.4</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Fig. 1. Change in eGFR from baseline with treatment. Main graph, over the whole 48-month study period; inset graph, over the first 3 months. Data are mean changes from baseline ± SE.

Analysis of slopes at each time point showed transitions from significant to insignificant values at 3 months and from insignificant to significant values at 21 months. Analysis of slopes at 1 week to 3 months, 6–21 months and 24–48 months confirmed that irbesartan initially increased the rate of ΔeGFR deterioration compared with placebo and
amlodipine but that after 6 months, the rate of ΔeGFR deterioration was slower in irbesartan-treated patients (Table 2a). The early decline with irbesartan appeared to be apparent in the first month of treatment only (Figure 1). Fitted model predictions generated overall estimated the rates of ΔeGFR change for these time periods (Table 2b), with estimated rates of ΔeGFR decline from 24 months of 2.34, 3.76 and 3.52 mL/min/1.73m²/year for irbesartan, amlodipine and placebo, respectively.

Analysis using the CKD-EPI equation [20] did not materially affect the results (Supplementary Table 2).

Moderators and mediators of treatment effect

Baseline CKD stage and ΔeGFR. Because at baseline only 29 patients had CKD Stage 1 and only 3 had CKD Stage 5, Stages 1 and 2 and Stages 4 and 5 were collapsed into single groupings for further analysis. Patient numbers in these groupings by treatment were as follows and showed no significant differences (χ² test = 3.368, d.f. = 4, P = 0.4098): Stages 1–2, placebo 139, amlodipine 128, irbesartan 120; Stage 3, placebo 316, amlodipine 328, irbesartan 351 and Stages 4–5, placebo 110, amlodipine 102, irbesartan 104.

The rate of decline in ΔeGFR was greater in those with earlier CKD stages (Figure 2a). Irbesartan slowed the rate of deterioration in ΔeGFR in all three baseline CKD stage groupings (Figure 2d). Relative to placebo, estimates for slope in patients with CKD Stages 1–2, Stage 3 and Stages 4–5 changed significantly in a positive direction with irbesartan (ΔeGFR slope 0.16090, P = 0.0020; 0.08770, P = 0.0061 and 0.11131, P = 0.0177, respectively) but not significantly with amlodipine. Adding a treatment-by-baseline CKD stage interaction term to the model was not significant, indicating that irbesartan reduced the rate of ΔeGFR deterioration irrespective of baseline CKD stage.

BP and ΔeGFR. Baseline BP and ΔeGFR. Higher baseline SBP increased both initial ΔeGFR deterioration at 1 week (ΔeGFR intercept −0.03312, P < 0.0001) and later rate of deterioration between 2 weeks and 48 months (ΔeGFR slope −0.00175, P = 0.0024). Adding a treatment-by-baseline SBP interaction term to the model had no significant effect, indicating that irbesartan reduced the rate of ΔeGFR deterioration irrespective of baseline SBP level. Inclusion of baseline DBP had no effect on the results.

Change in BP with treatment. Both ΔDBP and ΔSBP showed highly significant initial falls with irbesartan (ΔDBP and ΔSBP intercepts −3.30671 and −6.01053, respectively; both, P < 0.0001) and amlodipine (ΔDBP and ΔSBP intercepts −3.40545 and −4.55622, respectively; both, P < 0.0001) compared with placebo, as expected. However, subsequent to this initial decline, slopes remained parallel for all treatment groups (Figure 3).

Change in ΔSBP and ΔeGFR with treatment while controlling for baseline SBP. Given the greater decline in BP parameters with active treatments compared with placebo, the relative improvement in rate of ΔeGFR deterioration with irbesartan might have been explained by its BP lowering effect. To explore this, a mixed-effects analysis was performed entering baseline BP parameters, centred mean change from baseline BP parameters and treatment into the model as (i) main effects; (ii) the two-way interactions months-by-BP and BP-by-treatment and (iii) a three-way interaction term, months-by-BP-by-treatment (Supplementary Table 3).

The ΔSBP term demonstrated that at 1 week, there was a positive association with ΔSBP and improved ΔeGFR (ΔeGFR intercept 0.07146; P < 0.0001), but the Months:ΔSBP term showed that this effect became weaker over time (ΔeGFR slope −0.00115; P < 0.0001) (Supplementary Table 3). In addition, a significant interaction was noted between initial ΔSBP and irbesartan (ΔeGFR intercept 0.02831; P = 0.0002), suggesting that initial changes in SBP may partially mediate initial improvements in ΔeGFR with irbesartan (Supplementary Table 3). However, the Months:Baseline SBP slope term (−0.00201; P = 0.0008) showed that high baseline SBP continued to drive the rate of ΔeGFR
deterioration irrespective of baseline SBP and irbesartan (ΔeGFR intercept 0.00690, P = 0.00201; P = 0.0008) (Supplementary Table 3). However, the Months:Baseline SBP slope term (−0.00201; P = 0.0008) showed that high baseline SBP continued to drive the rate of ΔeGFR.

Table 2. Change in eGFR from baseline with irbesartan treatment: (a) mixed-effects model estimates from 1 week to 3 months, 6–21 months and 24–48 months and (b) fitted model predictions

<table>
<thead>
<tr>
<th>(a) Mixed-effects model</th>
<th>Estimatea</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo and amlodipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.06566</td>
<td>−0.28624 to 0.41757</td>
<td>Reference</td>
</tr>
<tr>
<td>Months</td>
<td>−0.71386</td>
<td>−0.77595 to −0.65177</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months²</td>
<td>0.01275</td>
<td>0.00948 to 0.01602</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months³</td>
<td>−0.00016</td>
<td>−0.00021 to −0.00012</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change from reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan (1 week)</td>
<td>0.52366</td>
<td>−0.01164 to 1.15896</td>
<td>0.1062</td>
</tr>
<tr>
<td>Months:Irbesartan (2–3 months)</td>
<td>−0.30967</td>
<td>−0.57001 to −0.04933</td>
<td>0.0197</td>
</tr>
<tr>
<td>Months:Irbesartan (6–21 months)</td>
<td>0.07408</td>
<td>0.02261 to 0.12555</td>
<td>0.0048</td>
</tr>
<tr>
<td>Months:Irbesartan (24–48 months)</td>
<td>0.09674</td>
<td>0.05076 to 0.14271</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(b) Model-derived predictions</td>
<td>eGFR monthly rate of change (mL/min/1.73m²)</td>
<td>6–21 months</td>
<td>24–48 months</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>−0.6319</td>
<td>−0.4112</td>
<td>−0.2932</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>−0.6462</td>
<td>−0.4296</td>
<td>−0.3134</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>−0.6850</td>
<td>−0.3354</td>
<td>−0.1947</td>
</tr>
</tbody>
</table>

*aUnit of estimate, change in eGFR (mL/min/1.73m²) per month.
deterioration, even after these initial treatment effects were taken into account. Finally, even after controlling for baseline SBP and ASBP in this analysis, the Months:Treatment with irbesartan term remained significant (ΔeGFR slope 0.10499, \( P = 0.0001 \)), indicating that irbesartan-induced changes in SBP did not mediate the long-term effect of irbesartan on rate of ΔeGFR change over time. No significant findings were observed for DBP parameters.

Proteinuria and ΔeGFR. Baseline proteinuria and ΔeGFR. Higher baseline proteinuria increased both initial ΔeGFR deterioration at 2 months (ΔeGFR intercept \(-1.29541; P < 0.0001\)) and later rate of deterioration between 3 and 48 months (ΔeGFR slope \(-0.16777; P < 0.0001\)). The addition of treatment-by-baseline proteinuria interaction moderator term was not significant, indicating that irbesartan reduced the rate of ΔeGFR deterioration irrespective of baseline proteinuria level.

Change in ΔProt with treatment. A mixed-effects analysis confirmed that irbesartan significantly decreased initial ΔProt at 2 months compared with placebo (ΔProt intercept \(-0.70141 \, g/24 \, h; P < 0.0001\)), whereas amlopidine treatment did not (ΔProt intercept 0.08136 \, g/24 \, h; \( P = 0.6404 \)) (Figure 4). From 3 to 48 months, the rate of change in proteinuria did not differ from placebo with either irbesartan (ΔProt slope \(-0.00023; P = 0.9758\) versus placebo) or amlopidine (ΔProt slope 0.00689; \( P = 0.3731\)). Thus, irbesartan reduced proteinuria at 2 months and this reduction was maintained from 3 to 48 months at a stable rate of \(\sim 1 \, g/24 \, h\) compared with amlopidine or placebo.

Change in ΔProt and ΔeGFR with treatment while controlling for baseline proteinuria. We addressed the possibility that the improvement in rate of ΔeGFR deterioration seen with irbesartan was explained by its proteinuria-lowering effect using the same methods as those for the BP analyses.

The ΔProt term demonstrated that at 2 months, there was a positive association with ΔProt and improved ΔeGFR (ΔeGFR intercept 0.90516; \( P < 0.0001\)), but the Month:\( \times \)ΔProt term showed that this effect became weaker over time (ΔeGFR slope \(-0.04036; P < 0.0001\)) (Supplementary Table 4). In addition, a significant interaction was noted between initial ΔProt and irbesartan (ΔeGFR intercept 0.29873; \( P = 0.0002\)), suggesting that initial changes in proteinuria may partially mediate improvements in ΔeGFR with irbesartan. However, high baseline...
proteinuria continued to drive ΔeGFR deterioration both initially (ΔeGFR intercept $-0.91389; P < 0.0001$) and the rate of deterioration over time (ΔeGFR slope $-0.18805; P < 0.0001$), even when accounting for initial treatment effects. After controlling for baseline proteinuria and ΔProt, the direct effect of irbesartan on reducing the rate of ΔeGFR deterioration over time was reduced in both magnitude and level of statistical significance (Month-3: Treatment with irbesartan ΔeGFR estimate for slope $0.06838; P = 0.0077$). This would suggest that irbesartan-induced proteinuria reduction partially mediated the effect of irbesartan on ΔeGFR, not only initially but also the rate of deterioration over time.

When patients were classified into six groups according to treatment-by-proteinuria change from baseline at EOS either above or below the threshold value of zero (Supplementary Table 5), the effect of treatment-by-proteinuria change was significant (d.f. = 5; $F = 4.73; P = 0.0003$). Only decreases in proteinuria with irbesartan improved ΔeGFR at EOS. Treatment-by-proteinuria change was then classified using the threshold of mean change from baseline at EOS ($-0.40 \text{g/24 h}$), instead of zero change. In the subgroup of patients with decreases in proteinuria below this threshold, irbesartan-treated patients still showed a relative improvement in ΔeGFR versus those receiving amlodipine [$2.74 \text{mL/min/1.73m}^2$; 95% confidence interval (CI) 1.10–5.19] and placebo ($3.15 \text{mL/min/1.73m}^2$; 95% CI 0.93–5.04), despite decreases in proteinuria below this threshold in all three treatment groups.

**Changes in serum potassium.** Although irbesartan significantly increased $K^+$ over the first 3 months of treatment compared with placebo and amlodipine ($\Delta K^+$ slope 1 week to 3 months 0.03555; $P < 0.0001$ versus amlodipine and placebo), change from 6 to 48 months remained stable, with no significant difference from change seen in the placebo group ($\Delta K^+$ slope 6–48 months 0.00014; $P = 0.8977$ versus placebo) (Figure 5). In contrast, following the initial decrease in $K^+$ with amlodipine ($\Delta K^+$ slope 1 week to 3 months $-0.03881; P < 0.0001$ versus placebo), from
In patients with established Type 2 diabetic nephropathy, the rate of change in ΔeGFR declined more slowly on irbesartan compared to amlodipine and placebo. The longer patients remained on irbesartan the slower the rate of loss of eGFR [model-derived estimates for 6–21 and 24–48 months were −0.3354 and −0.1947 mL/min/1.73m²/month (−4.02 and −2.34 mL/min/1.73m²/year), respectively]. Moreover, this benefit was seen irrespective of baseline CKD stage, BP or proteinuria level. The rate of decline for the patients on irbesartan was less than that previously reported for patients with Type 2 diabetic nephropathy and well-controlled hypertension [−0.4333 mL/min/1.73m²/month (−5.2 mL/min/1.73m²/year)] [21]. This analysis using eGFR provides information on average rates of progression that is not available when end points such as doubling of serum creatinine are used. Therefore, these data should help clinicians plan care for their patients who are approaching ESRD and supports the use of change in eGFR as an end point in future trials in progressive nephropathies.

Using the CKD-EPI equation [20] did not materially affect the analysis (Supplementary Table 2). This is perhaps not surprising as this modification of the original MDRD equation performed better for those with an eGFR >60 mL/min/1.73m², whereas patients in the current study had an average baseline eGFR of <50 mL/min/1.73m².

The long-term efficacy of irbesartan was independent of changes in BP. However, high baseline SBP was a driver for both initial and subsequent longer term rate of ΔeGFR deterioration, with the initial effect of irbesartan on ΔeGFR being partially mediated by reduced SBP (Supplementary Table 3). The implication of this finding is that patients should be initiated on irbesartan early in order to control BP and reduce the subsequent rate of decline of eGFR.

Irbesartan produced a rapid and sustained proteinuria reduction, which partially mediated treatment response both initially and over time (Supplementary Table 4). Only in irbesartan-treated patients was proteinuria reduction from baseline at EOS associated with less decline in ΔeGFR (Supplementary Table 5). However, when patients with an >0.4 g/24 h proteinuria reduction were compared across treatments, irbesartan still resulted in less decline in ΔeGFR compared to amlodipine or placebo.

The results of this post hoc analysis indicate that irbesartan slows the rate of deterioration in ΔeGFR through mechanisms partly related to initial and long-term proteinuria reduction and, to a lesser extent, initial reduction in SBP. These findings are consistent with previous studies which have shown the importance of reducing tubular protein overload [22, 23], glomerular capillary hypertension [24] and SBP [25, 26] for improved renal outcomes.

However, none of these potential mechanisms completely accounted for the long-term benefit of irbesartan on rate of ΔeGFR change. Irbesartan has been shown to reduce endothelial dysfunction, oxidative stress and inflammation [27–33]. In addition, RAAS blockade decreases collagen formation [34, 35] and improves kidney oxygenation [22]. These experimental results, together with RAAS-independent potentially renoprotective effects observed with some ARBs [36, 37], warrant further investigation in human diabetes.

It is clinically reassuring that, although irbesartan was associated with a greater initial rate of decline in ΔeGFR compared with amlodipine or placebo, the rate of loss of ΔeGFR was significantly reduced in the long term,
irrespective of baseline CKD stage. Moreover, the beneficial reduction in the rate of loss of AeGFR was greater as the study progressed. A recent publication from the RE-NAAAL investigators analysed outcome based upon stratification into tertiles of initial fall in eGFR [38]. They found that those in the highest tertile of initial loss showed improved long-term renal outcome compared to those with an initial rise. We could not confirm this finding in our patients on irbesartan based upon tertiles of initial fall (data not shown), but as a group, they did better over 4 years than those on amlodipine or placebo despite a greater initial loss of GFR. Patients with established Type 2 diabetic nephropathy should thus be started on treatment early and can be maintained safely long term.

Serum potassium levels rose initially on irbesartan but stabilized after 6 months in contrast to amlodipine-treated patients who, after an initial decline, showed a steady rise from 3 to 48 months. Therefore, potassium should be monitored at initiation or modification of irbesartan treatment but thereafter no more frequently than for any other antihypertensive agent or any other clinical indication.

This post hoc analysis of the IDNT, using eGFR as the principal outcome measure, confirmed that irbesartan significantly slowed the long-term rate of decline in eGFR compared to non-RAAS-based therapies, resulting in delayed progression towards ESRD by at least 33%. Irbesartan was equally effective irrespective of baseline CKD stage, and its benefit became stronger with longer duration of treatment, being only partly explained by reductions in BP and proteinuria. This analyses strongly support the early use of treatments which block the RAAS in the management of patients with established Type 2 diabetic nephropathy.

**Supplementary data**

Supplementary data are available online at http://ndt.oxfordjournals.org.

**Acknowledgements.** Medical writing and statistical assistance was provided by Paul Bassett, Fellow Royal Statistical Society, was funded by Sanofi-aventis and Bristol Myers Squibb. Statistical comments which block the RAAS in the management of patients being only partly explained by reductions in BP and proteinuria translates glomerular permselectivity into tertiles of initial fall (data not shown), but as a group, they did better over 4 years than those on amlodipine or placebo despite a greater initial loss of GFR. Patients with established Type 2 diabetic nephropathy should thus be started on treatment early and can be maintained safely long term.

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**References**


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