Aims
Limited data are available on the impact of renal function on the outcome of patients with atrial fibrillation (AF).

Methods and results
AMADEUS was a multicentre, randomized, open-label non-inferiority study that compared fixed-dose idraparinux with conventional anticoagulation by dose-adjusted vitamin K antagonists. We performed a post hoc analysis to assess the impact of renal function on the outcomes of anticoagulated AF patients. The primary efficacy outcome was the composite of stroke/systemic embolism (SE). The principal safety outcome of this analysis was major bleeding. We calculated c-indexes, reflecting the ability for discriminating diseased vs. non-diseased patients, and the net reclassification improvement (NRI, an index of inferior/superior performance of risk estimation scores). Of 4576 patients, 45 strokes and 103 major bleeding events occurred following an average follow-up of 325 ± 164 days. Patients with CrCl > 90 mL/min had an annual stroke/SE rate of 0.6% compared with 0.8% for those with CrCl 60–90 mL/min and 2.2% for those with CrCl < 60 mL/min (P < 0.001 for linear association). After adjusting for stroke risk factors, patients with CrCl < 60 mL/min had more than two-fold higher risk of stroke/SE and almost 60% higher risk of major bleeding compared with those with CrCl ≥ 60. In patients with the CHA2DS2-VASc score 1–2, CrCl < 60 mL/min was associated with eight-fold higher stroke risk. When added to the CHA2DS2-VASc or CHADS2 scores, CrCl < 60 mL/min did not improve the c-indexes for CHADS2 (P = 0.054) or CHA2DS2-VASc (P = 0.63) but resulted in significant NRI (0.26, P = 0.02) in this anticoagulated trial cohort.

Conclusion
Renal impairment (CrCl < 60 mL/min) doubles the risk of stroke and increased the risk of major bleeding by almost 60% in anticoagulated patients with AF. Renal impairment was additive to stroke risk prediction scores based on a significant NRI, but no significant improvement in discrimination ability (based on c-indexes) for CHA2DS2-VASc or CHADS2 was observed.

Keywords
Atrial fibrillation • Chronic kidney disease • Creatinine clearance • Stroke • Bleeding

Introduction
The prevalence of atrial fibrillation (AF) in end-stage chronic kidney disease (CKD) is high reaching 27% in patients on long-term haemodialysis.1–3 Even less advanced stages of CKD are associated with high prevalence of AF.4,5 Moreover, CKD is a common comorbidity among AF patients.6

Chronic kidney disease results in complex pathophysiological changes, involving both hypo- and hypercoagulability.7 An intimate relationship between CKD and oral anticoagulant (OAC)-related haemorrhagic events is well established. As a result, severe CKD is a predictor in most OAC-related bleeding risk estimation tools.8–13 On the other hand, patients with AF and advanced CKD have higher risk of thromboembolic events compared with AF patients with normal renal function.14 Current AF stroke risk stratification scores do not include CKD as a potential risk factor for thromboembolic events. Moreover, there is limited information on the impact of mild or moderate CKD on the
outcome(s) of anticoagulated patients with AF, and whether moderate-severe CKD improves the predictive value of stroke risk stratification.

The objective of this study was to evaluate the impact of renal function on the outcome of anticoagulated AF patients and second, to assess the additive prognostic value of moderate-severe CKD on the two widely used stroke risk prediction scores, the CHA2DS2VASC and CHADS2 scores.

Patients and methods

Study population

The study design of AMADEUS has been previously described. In brief, the AMADEUS trial was a multicentre, randomized, open-label non-inferiority study with blinded assessment of outcome that compared fixed-dose idraparinux with conventional anticoagulation by dose-adjusted oral vitamin K antagonist (VKA) therapy for the prevention of thromboembolism in patients with AF and an indication for long-term anticoagulation. Eligible patients had ECG-documented non-valvular AF and an indication for long-term anticoagulation based on the presence of at least one of the following risk factors: previous ischaemic stroke, transient ischaemic attack (TIA), or systemic embolism (SE), hypertension requiring drug treatment, left ventricular dysfunction, age over 75 years, or age 65–75 years with either diabetes mellitus or symptomatic coronary artery disease.

Exclusion criteria included inability to provide consent, contraindication to—or other requirement for—anticoagulation, calculated creatinine clearance (CrCl) rate of <10 ml/min, breastfeeding, (potential for) pregnancy, and recent or anticipated invasive procedures with potential for uncontrolled bleeding. Patients provided written informed consent; the protocol was approved by the appropriate ethics review boards.

Estimation of renal function

Renal function for each patient was estimated based on baseline serum creatinine using the three most widely used formulas: (i) the Cockcroft–Gault equation, (ii) the modification of diet in renal disease (MDRD) equation, and (iii) the CKD Epidemiology Collaboration (CKD-EPI) equation. Quartiles of serum creatinine were also used to stratify the AMADEUS population (that is, lower quartile \( \leq 80 \) mmol/L, second quartile 81–94 mmol/L, third quartile 95–109 mmol/L, and higher quartile \( \geq 110 \) mmol/L).

Study endpoints

This post hoc analysis of the AMADEUS trial used pooled data from both the VKA and idraparinux arms and included events that occurred in the randomization/on-treatment period (intention to treat analysis).

The principal safety outcome of the present analysis was major bleeding defined as bleeding that was fatal, intracranial, or affecting another critical anatomical site, or overt bleeding with a drop of haemoglobin \( \geq 20 \) g/L or requiring transfusion of two or more units of erythrocytes. The primary efficacy outcome of this analysis was the composite of all stroke (ischaemic, haemorrhagic, or undefined) or non-central nervous system (CNS) SE. Stroke was defined as a focal neurological deficit of sudden onset with a corresponding defect on brain imaging. Systemic embolism was confirmed by angiography, surgery, or autopsy. All suspected outcome events were classified by a central adjudication committee unaware of treatment assignment.

Statistical analysis

Means and standard deviations (SDs) or medians and inter-quartile ranges were calculated for continuous variables as appropriate. Frequencies and percentages were calculated for categorical variables. Continuous variables were analysed using the one-way ANOVA or Kruskal–Wallis test as appropriate. Categorical variables were analysed using chi-square tests.

We used Hosmer–Lemeshow goodness-of-fit statistics to assess models calibration with or without indices of renal function. The test assesses whether or not the observed event rates match expected event rates in subgroups of the model population. Overall models’ performance was assessed by Nagelkerke \( R^2 \). Nagelkerke \( R^2 \) provides an estimate of the proportion of the total variability in the outcome that is explained by the model. An \( R^2 \) near 1 indicates that a regression line fits the data well, while an \( R^2 \) close to 0 indicates a regression line does not fit the data very well.

Discriminatory performance was tested by receiver operating characteristic (ROC) analysis. The ROC curve is a plot of sensitivity vs. 1-specificity (often called the false-positive rate), and was constructed for each study endpoint in order to examine the predictive performance of each score. The c-index or area under the ROC curve, reflects the ability for discriminating diseased vs. non-diseased patients, and ranges from 0.5 (no discrimination) to a theoretical maximum of 1.0. Areas under the curve were compared using the non-parametric method proposed by DeLong et al. A significant improvement in c-indexes by the addition of indices of renal function would be indicative of an improvement in discrimination ability of the stroke scores.

Net reclassification improvement (NRI) was calculated as an index of inferior/superior performance of risk estimation scores. Net reclassification improvement is based on the assumption that a better score should assign higher risk to event positive subjects and less risk to event negative subjects. Event positive subjects assigned to higher risk category and event negative subjects assigned to a lower risk category by the new score are considered correctly reclassified. Event positive subjects assigned to lower risk category and event negative subjects assigned to higher risk category are considered misclassified. Net reclassification improvement is the difference between the percentages of correctly classified and misclassified subjects. To avoid confusion and biases that categorization of the data can cause, we calculated NRI for continuous scores.

To determine the independent prognostic value of indices of renal function, Cox proportional hazards models were used. Models were adjusted for treatment arms and depending on the outcome for stroke risk factors (age, previous stroke or TIA, treated hypertension) or major bleeding risk factors (age, previous stroke, uncontrolled hypertension, concomitant antiplatelet drugs, abnormal liver function, anaemia). A maximum of one candidate covariate per 10 events was used. Indices of renal function were introduced in the model as dichotomous or log transformed continuous variables. In the latter case, hazard ratios (HRs) refer to one unit of change of log transformed indices. A smoothing spline interpolation was applied for the graphic examination of the mortality risk (with 95% confidence intervals) across the range of kidney function.

Significance was indicated by a \( P \)-value \(<0.05\). Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software (version 17, SPSS, Inc., Chicago, IL, USA) and R software (www.r-project.org).

Results

The AMADEUS trial recruited 4576 patients; the mean age was 70 years, SD 9, 66.5% were men. Clinical and demographic characteristics of the population are summarized in Table 1.
In total, 45 strokes non-CNS SE and 103 major bleedings occurred in an average of 325 (SD 164) days follow-up period, corresponding to an annualized incidence of 1.1 and 2.5 events per 100 patient-years, respectively. Of note, there was no interaction between type of VKA and CrCl, nor any interaction between type of VKA and outcomes (stroke or bleeding).

### Chronic kidney disease staging

Baseline serum creatinine was available in 4554 (99.5%) patients. Based on Cockcroft–Gault CrCl 1470 (32.3%) patients had ‘more than mild CKD’, while 68 (1.5%) had ‘severe CKD’. Atrial fibrillation patients with more than mild CKD were more likely to be women, elderly with more comorbidities and the highest estimated risk for stroke (Table 1).

Different formulas for the estimation of renal function resulted in significant differences in the populations’ stratification, with the CKD-EPI formula stratifying more patients in the ‘more than mild CKD’ category (Supplementary material online, Table S1).

### Renal function and stroke/non-central nervous system-systemic embolism

Event rates in each stratum of renal function are shown in Table 2. Patients with CrCl >90 mL/min had an annual stroke/SE rate of 0.6% compared with 0.8% for those with CrCl 60–90 mL/min and 2.2% for those with CrCl < 60 mL/min (P < 0.001 for linear association). A similar association was observed when renal function was assessed by the MDRD or the CKD-EPI formulas or creatinine quartiles (data not shown).

When assessed as log transformed continues variables, all indices of renal function were independently associated with the outcome of stroke/non-CNS SE (Table 3). The association between HR for stroke/SE and CrCl using smoothing spline interpolation is shown in Figure 1.

In ROC analysis, CrCl demonstrated the highest discriminatory performance compared with other indices of renal function (c-index 0.66, 95% CI: 0.58–0.74 vs. 0.64 95% CI: 0.56–0.73, respectively). With a cut-off point of 57.8 mL/min presenting the highest overall predictive performance (sensitivity 0.58, specificity 0.71) for the outcome of stroke/non-CNS SE. In ROC analysis, CrCl as a continuous variable demonstrated a numerically higher discriminatory performance when compared with the CHADS2 score (c-index 0.66, 95% CI: 0.58–0.74 vs. 0.64 95% CI: 0.56–0.73, respectively).

After adjusting for demographic characteristics and co-morbid conditions, patients with CrCl <60 mL/min had a more than two-fold higher risk of stroke/SE compared with those with CrCl ≥60 mL/min (adjusted HR: 2.27, 95% CI: 1.14–4.52) (Figure 2).

### Renal function and risk stratification

Distribution of the study population by CKD stage in each CHA2DS2-VASc and CHADS2 category is illustrated in Figure 3.

‘More than mild CKD’ was present in 1.7% of patients with CHA2DS2-VASc score 1, 14.7% of patients with CHA2DS2-VASc score 2, 22% of patients with CHA2DS2-VASc score 3, and 49% of patients with CHA2DS2-VASc score 4 or above (P < 0.001 for linear association). A similar association was observed between CKD stage and CHADS2 score (P < 0.001 for linear association). In every CHA2DS2-VASc quartile, the presence of CrCl < 60 mL/min was associated with worse outcome (Figure 4). This was more pronounced in the lower CHA2DS2-VASc quartile (CHA2DS2-VASc 1–2), where CrCl
60 mL/min was associated with more than eight-fold higher risk for stroke/SE (relative risk 8.26; 95% CI: 1.68–40.6; \( P < 0.001 \)).

In ROC analysis, when CrCl \( \geq 60 \) mL/min was added to CHA2DS2VASc or CHADS2, there was no improvement in the c-indexes for the CHADS2 score (\( P = 0.054 \)) or CHA2DS2VASc (\( P = 0.63 \)) (Table 4).

Similar results were observed when CrCl was added in the calculation of CHADS2 and CHA2DS2VASc score weighed relative to its regression coefficient (two points for CrCl \( < 60 \) mL/min) (Supplementary material online, Figure S1). Based on giving two points for CrCl, c-indexes for CHA2DS2VASc score 0.70 (95% CI: 0.62–0.77) and 0.67 (95% CI: 0.60–0.75) for score with and without CrCl, respectively. C-indexes for CHADS2 score 0.69 (95% CI: 0.62–0.76) and 0.64 (95% CI: 0.56–0.73) with and without CrCl, respectively. CrCl, creatinine clearance; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

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Table 2  Event rates in each stage of chronic kidney disease

<table>
<thead>
<tr>
<th></th>
<th>Cockcroft–Gault CrCl</th>
<th>MDRD eGFR</th>
<th>CKD-EPI eGFR</th>
<th>Creatinine quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n ) /100 patient-years</td>
<td>( n ) /100 patient-years</td>
<td>( n ) /100 patient-years</td>
<td>( n ) /100 patient-years</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 90 )</td>
<td>6/0.6</td>
<td>2/0.4</td>
<td>0/0</td>
<td>8/0.9</td>
</tr>
<tr>
<td>( 60–89 )</td>
<td>13/0.8</td>
<td>17/0.8</td>
<td>19/0.9</td>
<td>8/0.9</td>
</tr>
<tr>
<td>( 30–59 )</td>
<td>26/2.2</td>
<td>25/1.9</td>
<td>24/1.6</td>
<td>10/1.1</td>
</tr>
<tr>
<td>( &lt;30 )</td>
<td>0/0</td>
<td>1/1.9</td>
<td>2/2.7</td>
<td>19/2.1</td>
</tr>
<tr>
<td>Total</td>
<td>45/45</td>
<td>45/45</td>
<td>45/45</td>
<td>45/45</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 90 )</td>
<td>15/1.3</td>
<td>7/1.6</td>
<td>3/0.9</td>
<td>21/2.2</td>
</tr>
<tr>
<td>( 60–89 )</td>
<td>38/2.4</td>
<td>53/2.4</td>
<td>52/2.5</td>
<td>21/2.3</td>
</tr>
<tr>
<td>( 30–59 )</td>
<td>48/3.8</td>
<td>42/3.2</td>
<td>45/2.9</td>
<td>24/2.6</td>
</tr>
<tr>
<td>( &lt;30 )</td>
<td>2/3.2</td>
<td>1/1.9</td>
<td>3/4.0</td>
<td>37/4.1</td>
</tr>
<tr>
<td>Total</td>
<td>103/103</td>
<td>103/103</td>
<td>103/103</td>
<td>103/103</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

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Table 3  Cox regression analysis: log transformed indices of renal function and event free survival

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>13.89</td>
<td>1.46–132.21</td>
<td>0.022</td>
</tr>
<tr>
<td>Cockcroft–Gault CrCl</td>
<td>0.06</td>
<td>0.01–0.44</td>
<td>0.005</td>
</tr>
<tr>
<td>MDRD eGFR</td>
<td>0.07</td>
<td>0.01–0.40</td>
<td>0.003</td>
</tr>
<tr>
<td>CKD-EPI eGFR</td>
<td>0.07</td>
<td>0.01–0.40</td>
<td>0.002</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>8.53</td>
<td>1.54–47.18</td>
<td>0.014</td>
</tr>
<tr>
<td>Cockcroft–Gault CrCl</td>
<td>0.14</td>
<td>0.04–0.51</td>
<td>0.003</td>
</tr>
<tr>
<td>MDRD eGFR</td>
<td>0.24</td>
<td>0.05–1.11</td>
<td>0.068</td>
</tr>
<tr>
<td>CKD-EPI eGFR</td>
<td>0.19</td>
<td>0.04–0.84</td>
<td>0.028</td>
</tr>
</tbody>
</table>

The model has been adjusted for age, previous stroke or transient ischaemic attack, treated hypertension and treatment arm. The model has been adjusted for age, previous stroke, uncontrolled hypertension, concomitant antplatelet drugs, abnormal liver function, anaemia, and treatment arm. CrCl, creatinine clearance; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

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**Figure 1** Unadjusted hazard ratio for stroke/non-central nervous system-systemic embolism (A) and major bleeding (B) by creatinine clearance as a continuous variable. The estimated hazard ratio (middle curve) is shown with the 95% confidence limits (upper and lower grey areas).
without CrCl, respectively. No improvement in the c-indexes for the CHADS2 score or CHA2DS2VASc was seen (both P = NS).

In reclassification analysis, adding CrCl in the CHA2DS2VASc or CHADS2 resulted in correct reclassification (higher score correctly assigned) of 58% of the event positive patients with misclassification (higher score wrongly assigned) of 32% of the event negative population, corresponding to a NRI of 26% (NRI: 0.26, 95% CI: 0.04–0.48, P = 0.02) (Table 4).

Renal function and major bleeding
A weaker association was observed between major bleeding rates and CKD stage. All renal function indices expect MDRD eGFR were independently associated with the outcome of major bleeding as log transformed continuous variables (Table 3). Patients with more than mild CKD (CrCl < 60 mL/min) had >50% higher risk of major bleeding compare with patients with CrCl ≥ 60 mL/min (HR: 1.58, 95% CI: 1.05–2.39, P = 0.027) (Figure 2). A similar association was established between major bleeding and the higher quartile of serum creatinine, but not MDRD or CKD-EPI eGFR.

Discussion
In a large cohort of patients with non-valvular AF on anticoagulation therapy, we found that patients with more than mild CKD (CrCl
60 mL/min) had more than two-fold higher risk for stroke/ non-CNS SE and almost 60% higher risk of major bleeding compare with patients with CrCl ≥ 60 mL/min. The risk associated with CKD was independent of clinical and demographic risk factors. Even in patients with CHA2DS2VASc scores 1–2, CrCl < 60 mL/min was associated with eight-fold higher stroke risk. Finally, CrCl < 60 mL/min did not improve the c-indexes for stroke risk prediction using CHA2DS2VASc or CHADS2; however, CKD indices did result in a significant NRI of both stroke risk scores.

The Cockcroft–Gault CrCl, a simple and widely used index of CKD, was independently associated with the risk of stroke/SE either as continues or dichotomous variable. In the AMADEUS cohort, a cut-off point for CrCl of 57.8 mL/min was associated with the highest sensitivity and specificity for the outcome of stroke/SE suggesting that ‘more than mild CKD’ (CrCl < 60 mL/min) could be used to refine stroke risk stratification of anticoagulated patients in AF. Nonetheless, CrCl < 60 mL/min did not significantly improve c-indexes of CHA2DS2VASc or CHADS2 scores. This is perhaps unsurprising given that CKD is commonly associated with the individual risk factors making up the components of the CHA2DS2VASc or CHADS2 scores. Of note, a weaker association was demonstrated between indices of renal function and major bleeding.

Cardiovascular disease is the leading cause of morbidity and mortality among patients with end-stage CKD.21–24 Nevertheless recent data suggest that the risk is not limited to end-stage renal disease. A number of studies have explored the relationship between CKD and cardiovascular endpoints by assessing kidney function as a continuous variable. Anavekar et al.25 reported that for each 10 unit reduction in eGFR.81 mL/min/1.73 m² was associated with a 10% increase in the relative risk of death or non-fatal CVD complications. In a different disease setting, Dries et al.26 reported a 24% increased risk of mortality for every 30 mL/min decrease in CrCl among patients with left ventricular systolic dysfunction.

Atrial fibrillation and renal disease share common predisposing factors, including age, hypertension, diabetes mellitus, and heart failure.2,22 Atrial fibrillation is also more frequent in patients with renal dysfunction.4 Limited data, however, are available on the risk of stroke among anticoagulated AF patients with CKD. Hoshino et al.23 recently reported an association between kidney damage and stroke types in Japanese patients, where the most frequent type of stroke among patients with CKD defined as eGFR < 60 mL/min/1.73 m² was cardioembolic infarction. Among patients with proteinuria only, the most frequent type of stroke was subcortical and subarachnoid haemorrhage.23 Moderate renal dysfunction has been also associated with a greater stroke severity and higher 30-day mortality after acute ischaemic stroke.24,25

Despite the close association between CKD and AF, patients with renal disease were under-represented in most studies that validated stroke risk stratification schemes, which ideally should be performed in non-anticoagulated unselected ‘real world’ cohorts with a wide range of renal (dys)function studied. Moreover, a variety of definitions for CKD have been used in these studies.

One recent ancillary analysis from the ROCKET-AF trial suggested that renal impairment (given 2 points) improved the predictive value of the CHADS2 score although difference in c-indexes was marginal27; however, the ROCKET-AF trial was a selected anticoagulation

### Table 4 Comparison of stroke risk prediction schemes

<table>
<thead>
<tr>
<th></th>
<th>CHA2DS2VASc Without CrCl</th>
<th>CHA2DS2VASc With CrCl</th>
<th>CHADS2 Without CrCl</th>
<th>CHADS2 With CrCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log likelihood</td>
<td>481.59</td>
<td>476.74</td>
<td>488.37</td>
<td>480.40</td>
</tr>
<tr>
<td>HL χ² (df)</td>
<td>5.00 (8)</td>
<td>8.08 (8)</td>
<td>2.63 (7)</td>
<td>2.88 (7)</td>
</tr>
<tr>
<td>Nagelkerke’s R²</td>
<td>0.05</td>
<td>0.06</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>c-index</td>
<td>0.70 (0.62–0.77)</td>
<td>0.73 (0.66–0.79)</td>
<td>0.66 (0.57–0.74)</td>
<td>0.71 (0.63–0.78)</td>
</tr>
<tr>
<td>NRI (continuous)</td>
<td>0.26 (0.04–0.48)</td>
<td>0.26 (0.04–0.48)</td>
<td>0.26 (0.04–0.48)</td>
<td>0.26 (0.04–0.48)</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; HL, Hosmer and Lemeshow; df, degrees of freedom; NRI, net reclassification improvement.
clinical trial cohort where only ‘high risk’ AF patients with CHADS2 ≥ 2 studied (mean CHADS2 score 3.5, where 55% were secondary prevention patients and those with CHADS2 = 2 were capped at 10%). Of note, severe renal impairment (CrCl < 30 mL/min) and CHADS2 0–1 were exclusion criteria in this trial. In the AMADEUS trial, however, the renal exclusion criterion from the study was CrCl < 10 mL/min, and importantly, patients with ≥1 stroke risk factors (including some patients CHADS2 = 0, e.g. age 65–74 years with symptomatic coronary artery disease) could be included. Thus, in contrast to the paper by Piccini et al., the present AMADEUS analysis is much more representative of the general AF population by including a wider spectrum of renal impairment and broader thromboembolic risk profile of AF patients, where we found that CrCl < 60 mL/min did not improve the c-indexes for either CHA2DS2VASc or CHADS2 scores.

While AMADEUS trial could even include some patients AF with a CHADS2 score = 0, such patients are not necessarily ‘low risk’ with stroke/TE rates ranging between 0.8 and 3.2%/year. Also, our study used CrCl to stratify the population in respect to CKD, but nevertheless all information was also available for the accurate calculation of eGFR based on the MDRD and the CKD-EPI formulas. In contrast, Piccini et al. assessed only CrCl as an index of renal impairment, and not MDRD or CKD-EPI estimated GFR which are the indices currently recommended by most international Chronic Kidney Disease societies. Finally, we assessed the prognostic importance of renal function on both bleeding and thromboembolic outcomes, while Piccini et al. did not assess the impact of renal impairment on the bleeding risk of patients with AF, nor did they assess incorporation of indices of renal function to the CHA2DS2VASc score, which is the scheme recommended by the 2012 ESC guidelines for stroke risk stratification in patients with AF. Thus, our study provides a much more complete assessment of the impact of renal impairment on the outcomes of patients with AF.

Effective prevention of stroke and SE in patients with AF and renal dysfunction poses a significant challenge. Recent studies have investigated the association between stroke and renal function in anticoagulated patients with AF. Indeed, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study confirmed that a lower level of eGFR was associated with a graded, increased risk of ischaemic stroke and other SE, independent of known risk factors in AF patients treated with warfarin. In the ATRIA study, the rate of thromboembolism off warfarin increased significantly with lower eGFR, ranging from 1.63 per 100 person-years for eGFR ≥ 60 mL/min/1.73 m² to 4.22 per 100 person-years for eGFR < 45 mL/min/1.73 m².

Our results also suggest that patients with CKD might benefit from more aggressive stroke prevention strategies. Such strategies include more intensive INR monitoring to ascertain strict INR control or more effective oral anticoagulation regimes (i.e. novel OACs, unless in very severe CKD) when indicated. Alternatively, left atrial appendage occlusion may be an option in patients at (very) high stroke and bleeding risk, but more data are clearly needed in AF patients with CKD.

Limitations
The AMADEUS study was not designed to assess the impact of renal function on outcomes of anticoagulated patients with AF. This cohort may not be adequately statistically powered to detect differences in all subgroups, and these are results of a post-hoc analysis and should be interpreted as such. The AMADEUS population was at relatively low risk of both ischaemic stroke and bleeding events compared with ‘real world’ patients. Patients at high risk of bleeding, and those with extremely severe CKD (CrCl < 10) were excluded from the AMADEUS study and thus the association of renal function indices and the risk of bleeding should be interpreted with some caution. Our previous study on the AMADEUS cohort was essentially a validation of bleeding risk scores, and the importance of individual clinical and demographic factors (particularly indices of renal impairment) on the risk of bleeding was not fully investigated, nor thromboembolic outcomes.

Risk estimation tools have been developed and validated in non-anticoagulated cohorts. Thus, their predictive value in well-managed anticoagulated populations (especially selected clinical trial cohorts) should be interpreted with some caveats. This is supported by the relatively low c-indexes (as a measure of the discrimination ability of a risk score) of both CHADS2 and CHA2DS2VASc in this particular cohort. Nonetheless, these scores can still be related to event risks, even in AF patients who are already taking OAC.

Nonetheless, it is possible that the risk associated with impaired renal function in non-anticoagulated populations is different, and further studies are required to establish whether CrCl-adjusted risk scores would have a similar performance in ‘real-world’ unselected populations, including non-anticoagulated AF populations. Finally, we calculated reclassification improvement for continuous scores, given that these scores were originally validated as a continuum. Calculating NRI for continuous scores provide reproducible, bias-free results but the clinical importance of improved classification based on continuous scores is less certain.

Conclusion
More than mild renal impairment (defined as CrCl < 60 mL/min) doubled the risk of stroke and increased the risk of major bleeding by almost 60%, in this anticoagulated AF cohort. Renal impairment (CrCl < 60 mL/min) was additive to stroke risk prediction scores based on a significant NRI but no improvement in c-indexes for CHA2DS2VASc or CHADS2 was observed.

Supplementary material
Supplementary material is available at European Heart Journal online.

Authors’ contributions
S.A. wrote the first version of the manuscript. S.A. performed the statistical analysis. G.Y.H.L. provided the study idea and performed critical revisions and drafting of the manuscript. All authors commented on and helped with revisions to the manuscripts.

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