Renal function and oral anticoagulant treatment of incident non-valvular atrial fibrillation: a retrospective study

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Aim: To describe the renal function of individuals newly diagnosed with non-valvular atrial fibrillation in England, and describe how oral anticoagulant (OAC) treatment varies according to renal function. **Patients & methods:** We identified a cohort of individuals with non-valvular atrial fibrillation ($n = 18,419$) and described their renal function at diagnosis and the prevalence of OAC treatment initiation by renal function. **Results:** 79% of individuals had some evidence of renal dysfunction with 12% having a glomerular filtration rate <30 ml/min/1.73 m². OAC treatment initiation in the 6 months following diagnosis was lower in individuals with severe renal dysfunction than in those with normal renal function. **Conclusion:** The high prevalence of renal dysfunction and low OAC treatment prevalence highlights the need for additional evidence regarding OACs in individuals with severe renal dysfunction.

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Atrial fibrillation (AF) is a common cardiac condition characterized by an irregular heartbeat (cardiac arrhythmia). The condition is associated with an increase in the risk of blood clots (thromboembolism) with AF patients having a fivefold increase in age-adjusted incidence of stroke [1]. Standard of care for the reduction of thromboembolic risk in AF includes treatment with oral anticoagulants (OACs) including vitamin K antagonists (VKAs; e.g., warfarin), and among individuals without a valvular etiology underlying their condition, one of the newer direct oral anticoagulants (DOACs; e.g., apixaban, rivaroxaban, dabigatran, edoxaban).

There is a strong association between AF and chronic kidney disease (CKD), with the prevalence of AF in those diagnosed with CKD reported to be two to three-times higher than that in the general population. Among those with CKD, decreasing kidney function is associated with increased thromboembolic risk [2,3], and patients with AF and moderate to severe CKD are at a higher risk of stroke or systemic thromboembolism than those without renal disease [4,5]. Among individuals with both AF and renal dysfunction there is therefore a need for effective prophylactic treatment for the prevention of stroke and systemic embolism.

Among individuals with AF and mild to moderate renal dysfunction, subgroup analyses from trials and observational studies appear to support the net benefit of VKAs over no OAC treatment [6–8]. Despite initial safety concerns regarding the use of DOACs in CKD patients due to their high renal elimination, the evidence increasingly suggests the net benefit of DOACs in these mild/moderate patients is similar to or better than that of VKAs [9–12]. As a result, treatment guidelines recommend that AF patients with mild/moderate renal dysfunction are treated with OACs [13].

Evidence to support the efficacy and safety of OACs in individuals with AF and severe renal dysfunction is lacking as this patient group have been routinely excluded from pivotal clinical trials in this field [14–16]. The limited data that are available in this patient group are observational in nature and have provided inconsistent findings,

with a number of studies suggesting an increased risk of bleeding in those using VKAs and DOACs, with the elevated risk observed lower in those on DOACs [6,17–19]. Despite the limited evidence, European guidelines state that those with moderate to severe CKD (glomerular filtration rate [GFR] ≥ 15 ml/min) can be safely treated with anticoagulants [13]. Given the lack of evidence on OAC-use in those with kidney failure (GFR < 15 ml/min), European guidelines call for further research in this patient group; however, US guidelines recommend warfarin treatment for these patients [20].

The observational nature of much of the evidence underlying treatment guidelines in individuals with renal dysfunction is likely to result in the heterogeneous real world management of these patients [20,21]. The objective of this study is therefore to describe renal function among individuals in England newly diagnosed with non-valvular atrial fibrillation (NVAf) and investigate whether OAC treatment is lower in those with poorer renal function. The results of the study will provide further insights into the relationship between AF and renal dysfunction, and the extent to which the limited evidence on the efficacy and safety of OACs in individuals with NVAf and CKD has impacted the management of thromboembolic risk in the patient population.

Methods

Data source

This study was carried out using a linked Clinical Practice Research Datalink (CPRD) – Hospital Episode Statistics (HES) dataset. This dataset links anonymized data from the medical records of patients registered with participating general practices (GPs) in England (the CPRD dataset) with administrative records regarding their clinical care in NHS hospitals (the Hospital Episode Statistics dataset). The dataset therefore includes longitudinal information on diagnoses, symptoms, laboratory tests and prescriptions issued by the GP in addition to information on referrals to specialists, hospital diagnoses, hospital procedures and deaths [21]. While the dataset does not capture private healthcare encounters and underrepresents certain geographic areas of the UK, it has been found to be a representative of the UK population with regard to sex, age and ethnicity [21]. The data source has been used extensively in drug safety and health services research resulting in over 2000 peer reviewed publications [22].

Study design & population

This was a descriptive population-based study in patients newly diagnosed with NVAf. The study population therefore consisted of individuals with an AF diagnosis recorded in their GP or hospital records between 2013 and 2017, and no prior record of AF or valvular disease in these sources. Patient follow-up in the study population began at the latest date of 01/01/2013, an age of 45 years, 1 year following registration at a CPRD practice or the date recording in a GP practice met recording standards. Patient follow-up ended at the earliest date of death, 31/12/2017, the date a patient transferred out of the practice or the last recorded data collection from the practice. Each individual's index date was set to 6 months following an individual's NVAf diagnosis to allow for clinical events occurring around the NVAf diagnosis to be captured.

Renal function

The renal function of patients in the study population at the time of their NVAf diagnosis was classified according to their creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR). In other words, data on the age, sex, weight and race of the study population was extracted from patients records and combined with the most recent serum creatinine recorded in the 12 months prior to the date of their NVAf diagnosis to calculate the CrCl using the Cockcroft–Gault equation [23] and eGFR based on the Chronic kidney Disease Epidemiology Collaboration (CKD-EPI) equation [24]. Patients without a serum creatinine or weight recording in the 12 months prior to diagnosis were classified as having missing CrCl/eGFR.

As we anticipated that missing data on serum creatinine and weight records would impact the completeness of the renal function measures outlined above, renal function was also classified using diagnostic codes related to chronic renal dysfunction. Specifically, we classified patients as having chronic renal dysfunction if they had a diagnosis of CKD, a diagnostic code consistent with end-stage renal disease (ESRD), two records indicative of dialysis recorded at least 3 months apart or a record related to kidney transplant recorded in the year prior to the index date.

Anticoagulant treatment

The first OAC prescription issued in the 6 months following an individual's NVAf diagnosis date was extracted and used to classify an individual's initial OAC treatment as being VKAs, dabigatran, apixaban, rivaroxaban or

edoxaban. Individuals without an OAC prescription in the 6 months following their index date were classified as having no OAC treatment.

Analysis

The renal function of the study population was described within each level of CrCl, eGFR, CKD, ESRD, dialysis and kidney transplant variables as the number and proportion of patients – overall and among only those – with a renal function measurement in the year prior to diagnosis. The number and percentage of individuals treated with an OAC treatment was described within each level of the renal function variables.

Sensitivity analyses explored the impact of extending the window for the ascertainment of GFR and serum creatinine records 2 years prior to the index date and weight records to 3 years either side of the GFR/serum creatinine record (sensitivity analysis 1). An additional sensitivity analysis explored the impact of extending the window to identify the first OAC prescription to 12 months post-diagnosis (sensitivity analysis 2). A further sensitivity analysis explored the impact of extending the window for ascertainment of diagnoses/procedure indicative of renal dysfunction to any time prior to diagnosis (sensitivity analysis 3).

Results

We identified 18,419 individuals with an incident NVAF diagnosis during the study period. 2991 (16%) had a CrCl ≤ 50 ml/min, 5382 (29%) had a CrCl between 50 and 95 ml/min, 2186 (12%) had a CrCl > 95 ml/min and 7860 (43%) did not have a serum creatinine and/or weight record in the year prior to diagnosis to inform the calculation of CrCl (Figure 1A). A total of 6009 (33%) had an eGFR < 60 ml/min/1.73 m², 7541 (41%) had an eGFR between 60 and 90 ml/min/1.73 m², 1895 (10%) had an eGFR > 90 ml/min/1.73 m² and 2974 (16%) did not have a serum creatinine record in the year prior to diagnosis to inform the calculation of eGFR. A total of 1857 (10%) had an eGFR indicative of severe renal dysfunction or kidney failure (eGFR < 30 ml/min/1.73 m²) (Figure 1B). Figure 1C & D illustrate the percentage in each renal function category when those with missing test results are excluded from the population. A sensitivity analysis extending the window for ascertainment of serum creatinine and weight records resulted in proportion with no CrCl and eGFR record reducing to 23 and 9%, respectively (sensitivity analysis 3).

A total of 1832 (10%) of individuals had a record indicative of CKD recorded in the year prior to diagnosis, 2133 (12%) had a diagnosis of ESRD, and 37 (0.2%) and 21 (0.1%) had records indicative of dialysis and kidney transplant respectively. Extending the window for identification of these variables to any time prior to diagnosis increased the estimated prevalence of CKD to 30% and of ESRD to 25% (Supplementary Data). Using these diagnostic records to impute missing test values resulted in an additional 1.5 and 4.7% of the total study population being categorized as having severe renal dysfunction based on eGFR and CrCl, respectively.

A total of 9998 (54.3%) of the 18,419 individuals in the study population were prescribed an OAC treatment in the 6 months following diagnosis. 5386 (29%) were prescribed a VKA, while 4612 (25%) were prescribed a DOAC. Rivaroxaban was the most commonly prescribed DOAC, followed by apixaban and dabigatran. Edoxaban use was low with only 32 individuals having a prescription in the 6 months following diagnosis (Table 1).

Table 1 also describes the treatment status of individuals across renal function indicators. The proportion of individuals receiving OAC treatment was approximately 15–20% lower in those with test results consistent with severe renal dysfunction (CrCl of < 30 ml/min and an eGFR < 30 ml/min/1.73 m²) than in those with results indicative of normal renal function or mild/moderate renal dysfunction. The prevalence of OAC treatment in those with no test results was lower than that observed for individuals with records indicative of normal to moderate renal function, suggesting these individuals may systematically differ from those with a normal renal function test. Similar trend in the prevalence of nontreatment with OACs observed across renal function groups was observed in the sensitivity analysis (Supplementary Data).

The proportion of individuals with a diagnosis of CKD who were treated with OACs was similar to the proportion treated in those without a CKD diagnosis. However, among those with evidence of an ESRD diagnosis, evidence of dialysis treatment or evidence of kidney transplantation, the prevalence of OAC treatment was 15–25% lower than the prevalence in those without such evidence (Table 2). Extending the window for identification of diagnoses to any time prior to the index date increased the prevalence of these conditions; however, differences in OAC treatment patterns remained similar (Supplementary Data).

While the use of OACs was lower in those with evidence of poorer renal function, no notable differences in the specific OACs used was observed across different levels of renal function. VKAs were the most prescribed type of

Figure 1. Baseline renal function described in terms of creatinine clearance and estimated glomerular filtration rate among newly diagnosed atrial fibrillation patients in England (2012–2017). (A & B) Include individuals with missing test data in the denominator for the calculation of percentages, while panels (C & D) exclude those with missing test data from the denominator. CrCl: Creatinine clearance; eGFR: Estimated glomerular filtration rate.

OAC treatment across all categories, followed closely by DOACs (taken as a class). Rivaroxaban and apixaban were the most commonly used DOACs across categories.

Discussion

In a real-world cohort of patients diagnosed with NVAf in England between 2013 and 2017, we report a high prevalence of moderate (27%) and severe renal dysfunction (12%) among those with baseline renal function measurements. The proportion of individuals initiating OAC treatment following diagnosis was up to 20% lower in those with severe renal dysfunction compared with those with normal renal function and those with mild/moderate renal dysfunction suggesting the current lack of evidence on the efficacy and safety of OAC treatments in this large group of patients has limited their treatment.

The prevalence of renal dysfunction in NVAf reported in the literature varies, with AF registries reporting figures of 8, 29, 39 and 40% for moderate to severe renal dysfunction ($\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$) and figures of 11, 6 and 4% for severe renal dysfunction ($\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$) [5,25–28]. Among those with baseline renal function measurements available, we report 39% of individuals as having eGFR test records or diagnostic codes consistent with moderate to severe renal dysfunction and 12% of individuals as having an eGFR $< 30 \text{ ml/min/1.73 m}^2$ or diagnostic codes indicative of this (Figure 1B). This compares well with a number of the above sources and with data from the ORBIT-AF registry in which 61% of the study population with baseline renal function measurements available were classified as not having CKD [28]. These findings therefore serve to further highlight the high prevalence of renal dysfunction in individuals diagnosed with NVAf. Where lower figures are reported for some of the registries, that may reflect the use of a 1-year period prevalence in our study compared

Table 1. Oral anticoagulant treatment prescribed following a non-valvular atrial fibrillation diagnosis according to renal function at baseline.

OAC type	>95	50–95	CrCl (ml/min) 30–49	15–29	<15	No test
Total	2186 (100%)	5382 (100%)	2337 (100%)	594 (100%)	60 (100%)	7860 (100%)
Apixaban	194 (8.9%)	541 (10.1%)	242 (10.4%)	57 (9.6%)	NR	628 (8%)
Rivaroxaban	319 (14.6%)	744 (13.8%)	292 (12.5%)	51 (8.6%)	5 (8.3%)	1000 (12.7%)
Dabigatran	NR	171 (3.2%)	54 (2.3%)	5 (0.8%)	NR	197 (2.5%)
Edoxaban	NR	8 (0.1%)	5 (0.2%)	NR	NR	13 (0.2%)
Vitamin K	660 (30.2%)	1847 (34.3%)	736 (31.5%)	152 (25.6%)	14 (23.3%)	1977 (25.2%)
No OAC	931 (42.6%)	2071 (38.5%)	1008 (43.1%)	329 (55.4%)	37 (61.7%)	4045 (51.5%)
Glomerular filtration rate (ml/min/1.73 m²)						
	90–200	60–89	30–59	15–29	<15	No test
Total	1895 (100%)	7541 (100%)	4152 (100%)	316 (100%)	1541 (100%)	2974 (100%)
Apixaban	172 (9.1%)	794 (10.5%)	465 (11.2%)	20 (6.3%)	53 (3.4%)	160 (5.4%)
Rivaroxaban	254 (13.4%)	1175 (15.6%)	565 (13.6%)	21 (6.6%)	130 (8.4%)	266 (8.9%)
Dabigatran	NR	228 (3%)	125 (3%)	NR	40 (2.6%)	65 (2.2%)
Edoxaban	NR	15 (0.2%)	10 (0.2%)	NR	NR	5 (0.2%)
Vitamin K	479 (25.3%)	2254 (29.9%)	1312 (31.6%)	97 (30.7%)	581 (37.7%)	663 (22.3%)
No OAC	943 (49.8%)	3075 (40.8%)	1675 (40.3%)	176 (55.7%)	737 (47.8%)	1815 (61%)

CPRD: Clinical Practice Research Datalink; CrCl: Creatinine clearance; NR: Not reported in order to suppress the publication of cell counts <5 in line with CPRD policy; OAC: Oral anticoagulant.

Table 2. Oral anticoagulant treatment prescribed following a non-valvular atrial fibrillation diagnosis according to renal diagnoses recorded at baseline.

OAC type	CKD		ESRD diagnosis		Dialysis		Kidney transplant	
	No	Yes	No	Yes	No	Yes	No	Yes
Total	16587 (100%)	1832 (100%)	16286 (100%)	2133 (100%)	18382 (100%)	37 (100%)	18398 (100%)	21 (100%)
Apixaban	1497 (9%)	167 (9.1%)	1505 (9.2%)	159 (7.5%)	1664 (9.1%)	NR	1664 (9%)	NR
Rivaroxaban	2191 (13.2%)	220 (12%)	2191 (13.5%)	220 (10.3%)	2411 (13.1%)	NR	2410 (13.1%)	NR
Dabigatran	468 (2.8%)	NR	480 (2.9%)	NR	505 (2.7%)	NR	505 (2.7%)	NR
Edoxaban	30 (0.2%)	NR	30 (0.2%)	NR	32 (0.2%)	NR	32 (0.2%)	NR
Vitamin K	4825 (29.1%)	561 (30.6%)	4945 (30.4%)	441 (20.7%)	5376 (29.2%)	10 (27%)	5380 (29.2%)	6 (28.6%)
No OAC	7576 (45.7%)	845 (46.1%)	7135 (43.8%)	1286 (60.3%)	8394 (45.7%)	27 (73%)	8407 (45.7%)	14 (66.7%)

CKD: Chronic kidney disease; CPRD: Clinical Practice Research Datalink; ESRD: End-stage renal disease; NR: Not reported in order to suppress the publication of cell counts <5 in line with CPRD policy; OAC: Oral anticoagulant.

with the point prevalence used in a number of the registry studies, or the selection of healthier individuals into the registries.

Limited data on the relationship between renal function and OAC treatment in the UK are available. The Royal College of General Practitioners (RCGP) Research and Surveillance Centre has reported that 34.7% of 6977 patients in England aged 65 years or older with a new diagnosis of AF between 2006 and 2016 and eGFR <50 ml/min/1.73m² were treated with an OAC in the 60 days post-diagnosis, and of these, 71.7% were treated with a VKA, 4.4% with rivaroxaban, 3.8% with apixaban, 1.0% with dabigatran and 0.05% with edoxaban [29]. In the present study, we found that 55% of patients were treated with an OAC. The discrepancy between our results and those of the RCGP may reflect an increase in treatment prevalence over time and the use of a longer period post-diagnosis to identify treatment initiation. Unlike our study, the RCGP study did not provide a breakdown of results across renal function groups and did not provide data in those with normal renal function as a reference. We therefore believe our study to provide the most thorough and up-to-date assessment of the association between renal function and OAC treatment of NVAF in England currently available in the literature. Outside the UK, approximately 30% of individuals with AF and advanced CKD/ESRD/dialysis in the USA have been reported to receive warfarin, and up to 10% receiving DOACs [30–32]. Data from US and global AF registries report higher OAC treatment prevalence of 70–80%; however, the US registry included prevalent patients and used a 3 year

follow-up period to identify treatments, while the global registry excluded patients without at least one stroke risk factor [28–31,33,34]. The higher treatment prevalence observed in a number of these registries may reflect the inclusion of prevalent patients and use of different time frames to identify treatment rather than a true geographical difference in the prevalence of treatment.

That the majority of individuals in England with severe renal dysfunction and indicators of ESRD are not being treated with OACs is somewhat unsurprising given the bleeding risk observed in this patient group and the lack of guidelines regarding their use [6,17–19]. Notably, in US guidelines for the management of AF published in 2014, a class IIa recommendation that warfarin treatment of patients with severe renal dysfunction was considered reasonable was issued, based on the results of a US cohort study by Winkelmayr *et al.* [35]. This recommendation, combined with the growing pool of data supporting the use of warfarin in this patient population, [6] is likely to underlie the fact that VKAs were used in 21% of ESRD patients, 27% of dialysis patients and 29% of kidney transplant patients. That this proportion is not higher is likely a result of the safety issues noted in some of these observational studies and the lack of a recommendation in European and English guidelines similar to that in the US guidelines [13,36]. It is also notable that despite the lack of data on DOACs in severe renal dysfunction, almost as many individuals with ESRD received DOACs as VKAs, primarily rivaroxaban and apixaban. Overall, the findings in this patient group support the ongoing calls for greater evidence to support OAC prescribing in severe renal dysfunction and ESRD.

In contrast, our findings in those with mild and moderate renal dysfunction suggest that the growing evidence base and recommendations supporting the effectiveness and safety of VKAs and DOACs in NVAf patients with mild/moderate renal dysfunction is influencing practice, with the proportion receiving OAC treatment being broadly in line with those with normal renal function.

The study is subject to a number of limitations, these have been explored quantitatively via sensitivity analysis where possible. For example, the results of serum creatinine tests carried out in inpatient or outpatient settings are not captured within the linked datasets we have used. It is therefore possible that some of the individuals defined as having no serum creatinine recording in the 12 months prior to the NVAf diagnosis had recordings made in these alternative settings. One might expect this to be a greater issue for those with severe renal dysfunction as they will be managed in these settings more regularly (e.g., for dialysis). Our binary outcome measure of ESRD supports this hypothesis, as the number of individuals with clinical evidence of ESRD is higher than the number with CrCl/eGFR records indicative of this condition. We therefore suggest that the findings for the binary ESRD outcome are interpreted as a more robust measure of treatment in those with ESRD than the CrCl or eGFR data. In order to accurately capture an individual's serum creatinine and the weight for use in the calculation of CrCl and eGFR, we required records within the previous 12 months to be available. A failure to measure serum creatinine at diagnosis and annually as recommended, [22] may also contribute to the proportion with missing test results. A sensitivity analysis extended the period for identification of serum creatinine to 2 years and for identification of weight records to 3 years resulting in an additional 3690 CrCl records and 1285 GFR records being available for analysis. This decreased the treatment prevalence among those with test records slightly but did not alter the overall interpretation of the findings.

Data on inpatient or outpatient prescribing is also not available in the linked dataset we have used; as a result, we used a 6-month period post-diagnosis to identify initial treatment status. Despite this, some of the individuals defined as having no OAC prescribed within this period may have received prescriptions in one of these alternative settings during this period. The sensitivity analysis extending the window for prescription ascertainment to 12 months suggests that this has little impact on the results underlying our key conclusions.

Finally, it should also be noted that the current study is descriptive in nature and does not explore the relationship between the characteristics of individuals with different renal function and OAC treatment initiation. It is therefore possible that the pattern of OAC treatment initiation we observe across renal function categories is driven by differences in the prevalence of risk factors for stroke and bleeding or other factors that impact OAC treatment decisions.

Conclusion

In conclusion, among a cohort of newly diagnosed NVAf patients in England, the prevalence of renal dysfunction was high and the majority of patients with renal dysfunction received no OAC treatment following their NVAf diagnosis. The use of DOACs in those with severe renal dysfunction was particularly low. These findings highlight

the pressing need for additional evidence and guidelines regarding the efficacy and safety of OACs in individuals with CKD, particularly among those with severe renal dysfunction.

Future perspective

As experience with the use of OACs in individuals with renal dysfunction grows, so too will the amount of observational evidence available on the clinical effectiveness and safety of these drugs. Should this evidence suggest that the net benefit of OACs in individuals with AF and severe renal dysfunction is favorable, then the low treatment prevalence observed in the patient group in this study may rise in the future. Initial data suggest that a net benefit is more likely to be substantiated for specific DOACs than VKAs; therefore, increases in treatment prevalence may be observed for these DOACs only. Despite this, in the absence of randomised data supporting the net benefit of OACs in this patient group and/or strong recommendations in clinical guidelines, OAC treatment prevalence in those with renal dysfunction is likely to remain lower than that observed in individuals with normal renal function.

Summary points

- Oral anticoagulant (OAC) treatment of atrial fibrillation (AF) patients with renal dysfunction is complicated by a lack of evidence.
- We used a linked Clinical Practice Research Datalink (CPRD) – Hospital Episode Statistics (HES) dataset to identify 18,419 patients with non-valvular atrial fibrillation (NVAF).
- We found 79% of individuals with some evidence of renal dysfunction among those in whom 12% had evidence of severe renal dysfunction/failure.
- The proportion of individuals receiving OAC treatment was approximately 15–20% lower in those with test results consistent with severe renal dysfunction (creatinine clearance [CrCl] of <30 ml/min and an eGFR <30 ml/min/1.73 m²) than in those with results indicative of normal renal function or mild/moderate renal dysfunction.
- While use of OACs were lower in those with evidence of poorer renal function, no notable differences in the specific OACs used were observed across different levels of renal function. Vitamin K antagonist (VKAs) were the most prescribed type of OAC treatment across all categories, followed closely by direct oral anticoagulants (DOACs) (taken as a class). Rivaroxaban and apixaban were the most commonly used DOACs across categories.
- The proportion of individuals initiating OAC treatment following diagnosis was up to 20% lower in those with severe renal dysfunction compared with those with normal renal function and those with mild/moderate renal dysfunction.
- The bleeding risk in individuals with severe renal dysfunction and indicators of ESRD would explain why this group of patients are not being treated with OACs due to the lack of guidelines regarding their use.
- Limitations were identified and explored quantitatively via sensitivity analysis where possible. None of these analyses impacted the key conclusions.
- The findings of this study highlight the pressing need for additional evidence and guidelines regarding the efficacy and safety of OACs in individuals with chronic kidney disease (CKD), particularly among those with severe renal dysfunction.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/suppl/10.2217/fca-2019-0012

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Ethical conduct of research

The authors state that they have obtained appropriate approval from the CPRD Independent Scientific Advisory Committee (ISAC), and as such, have ethical approval for this study under the CPRD's Multicentre Research Ethics Committee (MREC) approval to undertake observational studies and external data linkages with HES.

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