Impact of glomerular filtration estimate on bleeding risk in very old patients treated with vitamin K antagonists

Results of EPICA study on the behalf of FCSA (Italian Federation of Anticoagulation Clinics)

Daniela Poli[1]; Emilia Antonucci[2]; Maria Zanazzi[3]; Elisa Grifoni[2]; Sophie Testa[4]; Walter Ageno[5]; Gualtiero Palareti[6]

[1]Thrombosis Centre Department of Heart and Vessels, AOU-Careggi, Florence, Italy; [2]Department of Medical and Surgical Critical Care University of Florence, Italy; [3]Renal Unit, AOU-Careggi, Florence, Italy; [4]Haemostasis and Thrombosis Centre A O Istituti Ospitalieri di Cremona, Cremona, Italy; [5]Department of Clinical Medicine University of Insubria, Varese, Italy; [6]Department of Angiology and Blood Coagulation "Marino Golinelli", University Hospital S. Orsola-Malpighi, Bologna, Italy

Summary

Vitamin K antagonists (VKA) therapy is increasingly used in elderly for prevention of venous thromboembolism (VTE) and of stroke in atrial fibrillation (AF). Glomerular filtration rate (GFR), usually estimated from different equations, decreases progressively with age and it is a risk factor for bleeding. In the frame of the EPICA study, a multicentre prospective observational study including 4,093 patients ≥80 years naïve to VKA treated for AF or after VTE, we performed this ancillary study to evaluate the prevalence of chronic kidney diseases (CKD) by estimated GFR (eGFR). Incidence of bleedings was recorded and bleeding risk was evaluated in relation to eGFR calculated by Cockroft-Gault (C-G); Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. In addition, the agreement among the three eGFR formulas was evaluated. We recorded 179 major bleedings (rate 1.87 x100 patient-years [py]), 26 fatal (rate 0.27 x100 py). Moderate CKD was detected in 69.3%, 59.3% and 47.0% and severe CKD in 5.8%, 7.4% and 10.0% of cases by C-G, MDRD and CKD-EPI, respectively. Bleeding risk was higher in patients with severe CKD irrespective of the applied equation. This study confirms that CKD represents an independent risk factor for bleeding and that a wide proportion of elderly on VKA had severe or moderate CKD, suggesting the need for frequent monitoring. Although the different available equations yield different eGFR, all appear to similarly predict the risk of major bleeding.

Keywords

Bleeding, elderly, glomerular filtration rate, VKA treatment

Correspondence to:
Daniela Poli, MD
Centro Trombosi
Viale Morgagni, 85–50134
Firenze, Italy
Tel.: +39 055 7949433, Fax: +39 055 7946218
E-mail: polida@aou-careggi.toscana.it

* Collaborators listed in full in the Appendix.

Received: October 20, 2011
Accepted after major revision: April 9, 2012
Prepublished online: April 26, 2012
doi:10.1160/TH11-10-0721
Thromb Haemost 2012; 107: 1100–1106

Introduction

Oral anticoagulant therapy with vitamin K antagonists (VKA) is increasingly used for the prevention and treatment of vascular diseases. Its effectiveness has been clearly established for the secondary prevention of venous thromboembolism (VTE), and for the prevention of systemic embolism in patients with atrial fibrillation (AF). Because the incidence of both VTE and AF increases with age, there are a considerable number of elderly patients having a clear indication for VKA treatment. In particular, data indicating that aspirin treatment is not protective of stroke in AF patients and results in an appreciable risk of bleeding (1, 2), has led to an increase of AF patients being treated with VKA, even if they are very old. It is well known that glomerular filtration rate (GFR) decreases progressively with age (3), and an increasing proportion of the general population has chronic kidney disease (CKD) which has been recognised as a 'silent epidemic' (4). In 2008, Rosamond et al. (5) reported an estimated prevalence of CKD of 16.8% in the general US population, including stages I to IV. However, this prevalence rose to 39.4% when only subjects aged older than 60 years were considered. The prescription of VKA, especially in the elderly, is a major concern for clinicians due the fear of bleeding. Many risk factors for bleeding and a number of potential contraindications for the use of VKA are common in elderly patients, in particular renal failure is considered as a risk factor for bleeding and is included in several models of stratification of bleeding risk (6–8). The use of bleeding risk estimation models is suggested by clinical practice guidelines (9, 10); however, no clear indication is reported for the definition of renal failure. GFR is the fundamental parameter of renal function and it is often estimated from different equations (11–14) that include serum creatinine levels as an important variable, and a single GFR cut-off of 60 ml/min/1.73 m^2 for the definition of chronic kidney disease is currently recommended (15). Severe CKD is defined when GFR is less than 30 ml/min/1.73

m^2. However, the different available equations for GFR estimate (eGFR) yield different results in the elderly (16, 17) with over-estimation of GFR in some cases, and there is uncertainty on which formula should be preferred in very old patients. We have previously published the results of the EPICA Study (18), a large multicentre prospective observational study reporting the bleeding risk of very elderly patients treated with VKA . This is an ancillary study performed to evaluate the prevalence of CKD among patients enrolled in the EPICA study, and the incidence of bleeding events in relation to renal function. In addition, we estimate CKD by using three of the most commonly used eGFR formulas evaluating their agreement.

Methods

Centres

Twenty-seven Centers affiliated to the Italian Federation of Anticoagulation Clinics (FCSA) participated in the study. FCSA Centres are required to give patients who start treatment adequate education on treatment purpose, risk of complications, information about international normalised ratio (INR) values and treatment management. They follow-up patients by periodic INR measurements, establish the date for the subsequent visits, prescribe the daily VKA dosages, monitor and record changes in patients habits, diet, co-medications, intercurrent illnesses, and bleeding as well as thrombotic complications on the basis of chart review and patients' interview. All Centres take part in the specifically designed laboratory external quality control program, which runs three times yearly and uses lyophilised plasma samples obtained from anticoagulated patients (19).

Patients

The present prospective observational study included 4,093 very old patients who started VKA treatment after the age of 80 years for thromboprophylaxis of AF or after VTE (first event or recurrence). All patients were maintained at intended therapeutic range of 2.0–3.0 INR. Patients' demographics, indications for VKA and clinical data were collected. Patients were classified as hypertensive if they were taking medications to lower blood pressure. Diabetes mellitus was defined according to American Diabetes Association Criteria (20). Coronary artery disease was defined on the basis of a history of myocardial infarction or stable and unstable angina. Heart failure was defined as the presence of signs and symptoms of either right or left ventricular failure or both, confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction. Patients who had more than two episodes of accidental fall in the last year were defined as "at high risk for fall".

Quality of anticoagulation was calculated as time in therapeutic range (TTR) using the linear interpolation method by Rosendaal et al. (21). This calculation started at the beginning of treatment.

Follow-up and end-points

Follow-up visits were scheduled every 2–4 weeks for INR monitoring. Patients who missed check-ups for more than two months were contacted (personally or through their family or general practitioner) and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. Deaths of all causes were recorded.

Definition for major bleeding is the following: fatal, intracranial (documented by imaging), ocular causing blindness, articular or retroperitoneal; bleeding requiring surgery or invasive manoeuvre, or transfusion of more than two blood units or when haemoglobin was reduced by >2 g/dl. All cases of clinically relevant bleeding events which were not classified as major were considered as 'minor' (20, 22). Follow-up was stopped after the first major bleed occurred, after the cessation of oral anticoagulation, or when a patient was no longer monitored by the participating centre.

Estimated GFR (eGFR) formulas

As an ancillary study, we collect serum creatinine levels measured by local hospital laboratories and body weight, at enrolment, when available. The inter-laboratory variability of creatinine measurement has been calculated of 7% for values around 1.5 mg/dl in Italian laboratories (unpublished data from External Quality Control Program of the Emilia Romagna Region). Creatinine clearance was calculated by the Cockroft-Gault formula (C-G) (11); the Modification of Diet in Renal Disease (MDRD) equation (12, 13); and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (14). Renal failure was defined as a calculated creatinine clearance <30 ml/min/1.73 m^2.

Statistical analysis

The SPSS statistical software package (Statistical Package for Social Sciences, Chicago, IL, USA, software for Windows; version 11.5) was used for data processing. We used descriptive analysis expressed as median and interquartile range (IQR). Incidence rates of adverse events were calculated as the number of events per 100 patients/years (py) of observation. For this calculation observation started at the beginning of follow-up and ended when patients experienced a major outcome or were censored.

Following a test of statistical normality, analyses were performed using Fisher's exact test (categorical data), unpaired t-test (parametric data) and Mann-Whitney test (non-parametric data). A

Table 1: Clinical characteristics of the patients.

N	4,093
Males n (%)	1,762 (43)
Median (range) age	84 (80–102)
Follow-up period (years)	9603
Mean follow-up period (years) (SD)	2.35 (2.1)
Indication for VKA treatment (%)	
Atrial fibrillation	3015 (73.7)
Venous thrombembolism	1078 (26.3)
Mean serum creatinine mg/dl (SD)	1.07 (0.41)
Serum creatinine >1.5 mg/dl	380/3171 (12.0)
Antiplatelets drugs	353 (9.3)
N. of drugs associated (≥3)	2365 (62.0)
Time in therapeutic range (IQR)	62 (49–75)
Past medical history	
Heart failure	890 (22.9)
Hypertension	2850 (72.3)
Diabetes	663 (17.0)
Coronary artery disease/ Peripheral artery disease	835 (21.9)
Cancer	534 (13.9)
Previous stroke/TIA	699 (17.1)

Data are expressed as n(%), mean (SD) or median (IQR). SD= standard deviation ; IQR= interquartile range; TIA, transient ischaemic attack.

Table 2: Risk factors associated to bleeding events: Univariate analysis.

	OR	95% CI	P-value
Male sex	1.41	1.04–1.92	0.02
Previous TIA/stroke	1.33	0.92–1.90	0.10
Hypertension	1.40	0.97–2.06	0.06
History of bleeding	5.41	3.29–8.50	<0.0001
Prior gastrointestinal bleeding	5.77	3.08–9.96	<0.0001
Prior cerebral bleeding	3.29	0.67–9.79	0.08
Renal failure (serum creatinine ≥1.5 mg/dl)	1.67	1.04–2.60	0.02
TTR <60% (*)	1.25	0.91–1.70	0.14
Active cancer	2.81	1.80–4.25	<0.0001
Antiplatelet use	1.32	0.77–2.14	0.25
History of falls	2.95	1.79–4.66	<0.0001
Co-medications (≥3 drugs)	1.43	1.01–2.05	0.04

(*) TTR=time in therapeutic range; OR, odds ratio; CI, confidence interval; TIA, transient ischaemic attack.

univariate analysis and a Cox regression analysis, were used to ascertain which factors were significantly associated with the risk of bleeding with VKA. All odds ratios (OR) are given with their 95% confidence intervals (CI) and a two-sided value of $p<0.05$ was chosen for statistical significance.

The 2x2 agreement tables among the different eGFR equations considered were used for the qualitative analysis. Agreement between the different tests was determined by *k* statistics, and 95% CIs were calculated.

Results

We enrolled and prospectively followed-up 4,093 patients (1,762 males, 43%) who started VKA treatment at the age of 80 years or older for stroke prevention in AF or for secondary prevention after VTE. The total observation period was 9,603 py and the median age of the patients at the beginning of follow-up was 84 years (range 80–102). Clinical characteristics of the entire population are reported in ▶Table 1. Creatinine levels at enrolment were available for 3,171 patients (77.5%) and body weight for 2,474 patients (60.4%). Mean serum creatinine levels of the whole population were 1.07 ± 0.41 mg/dl, and 12% of patients had serum creatinine values >1.5 mg/dl (▶Table 1). During follow-up, 385 patients died (total mortality rate 4.0 per 100 py): 26 patients (6.8%) because of haemorrhagic complications, 112 patients (29.1%) because of cardiovascular disease, 34 (8.8%) because of sudden death, 12 (3.1%) because of ischaemic stroke, 56 (14.5%) because of cancer, and 145 patients (37.7%) for other diseases not related to VKA treatment. In the whole population, TTR was 62% (IQR 49–75).

Bleeding events

During the whole observation period, 179 major bleedings were recorded (rate 1.87 x100 py), of which 26 were fatal (rate 0.27 x100 py) and 53 were intracranial (rate 0.55 x100 py). Risk factors significantly associated to bleeding at univariate analysis are reported in ▶Table 2. A history of bleeding, active cancer, and a history of falls were all independently associated with major haemorrhage after multivariable Cox regression ($p < 0.001$ for all three) (▶Table 3). Further, we performed a Cox regression analysis adjusted for the same variables, but defining renal failure as eGFR<30 ml/min/1.73 m^2, calculated with the three formulas considered. Again, history of bleeding, active cancer, and a history of falls were all independently associated with major haemorrhage (data not shown). Renal failure showed a hazard ratio (HR) for bleeding of 1.5 (95% CI 0.8–2.6; p=0.1) with C-G, 1.6 (95% CI 1.0–2.7; p=0.067) with MDRD and 1.7 (95% CI 1.0–3.1; p=0.057) with CKD-EPI.

Table 3: Risk factors associated to bleeding events: Multivariate Cox regression analysis.

	HR	95% CI	P-value
Male sex	1.37	0.9–1.9	0.08
History of bleeding	5.79	3.5–9.5	0.000
Renal failure (serum creatinine ≥1.5 mg/dl)	1.24	0.8–2.0	0.3
Active cancer	2.88	1.8–4.6	0.000
History of falls	2.97	1.7–5.3	0.000
Co-medications (≥3 drugs)	1.28	0.9–1.9	0.2

HR, hazard ratio; CI, confidence interval.

eGFR formulas

Bleeding rate was higher in patients with eGFR<30 ml/min/1.73 m^2 with respect to patients with eGFR ≥30 ml/min/1.73 m^2, irrespective of the applied equation (relative risk [RR] ranging from 1.86 to 2.11, all statistically significant) (▶Table 4). In ▶Table 4, ORs for bleeding risk in relation to eGFR estimated with the three used formulas are reported, by using eGFR>60 ml/min/1.73 m^2 as the reference.

▶Table 5 reports the distribution of patients in relation to eGFR according to the three different formulas. Based on the C-G equation, only 20.7% of patients had normal renal function (eGFR>60 ml/min/1.73 m^2), as opposed to 33.3% according to MDRD and 47.2% according to CKD-EPI equations. The *k* value among the three formulas is reported in ▶Table 5.

Discussion

To our knowledge, this is the largest study to assess the association between bleeding and renal function in a population of very elderly patients on VKA treatment with a long-term follow-up. As previously reported (18), the rate of major bleedings recorded in this study was 1.87 x100 py, slightly lower than that previously reported in a study conducted in a similar setting (23). Nevertheless, patients included in this study were followed from the beginning of VKA treatment, therefore including the induction phase of the treatment, which is associated with the highest risk for bleeding (24). Our data show that renal failure, irrelevant of the method used to evaluate it, is associated with an increased risk for bleeding, even if not statistically significant. However, it should be noted that when renal failure is evaluated as eGFR calculated with MDRD and CKD-EPI formulas, a trend to significance was found. Moreover, when we considered the incidence of adverse events in relation to time of exposure to VKA, eGFR<30 ml/min/1.73 m^2 is associated with an increased rate of major bleedings, independent of the equation used to estimate GFR. The finding that in our data renal failure fails to be independently associated with bleeding risk seems in contrast with the general consensus that renal failure is a risk factor for bleeding. Nevertheless, this parameter is commonly considered a risk factor for bleeding; therefore, a clear definition is needed. Serum creatinine levels are inadequate to estimate the degree of renal failure in the elderly (25, 26); with a very low sensitivity in particular in women (24), a correct estimation of the GFR becomes crucial to timely identify this important risk factor. In clinical practice, GFR is usually estimated from equations that include both creatinine levels and age as important variables. Unfortunately, none of the available equations for eGFR has been validated in very elderly patients, and no clear indication exists about which formula is best used for optimal estimation of kidney function in the elderly (17, 27, 28). In this study population of patients aged 80 years or older we found that as many as 5.8% to 10% of our ambulatory patients have severe CKD, whilst the rate of patients with a normal renal function was small, variable between 20.7% when renal function was estimated with the C-G formula to 47.2% when was estimated with the CKD-EPI equation. Chronic renal insufficiency has been recognised as a 'silent epidemic' (4, 5), and its

Table 4: Bleeding rates in relation to eGFR and ORs for bleeding risk in relation to eGFR with the three considered formulas for GFR estimate.

	Bleeding events	Bleeds x100 py	RR (95%CI)	P-value	OR (95% CI)	P-value
Cockcroft-Gault (ml/min x1.73 m^2)	108	2.0				
< 30	18	3.4	1.86 (1.1–3.1)	0.03	1.4 (0.7–2.6)	0.3
30–60	65	1.7	0.65 (0.4–1.0)	0.04	0.8 (0.5–1.2)	0.3
>60	25	2.4	1.16 (0.9–1.8)	0.51	1 (ref)	
MDRD (ml/min x1.73 m^2)	136	1.8				
< 30	19	3.8	2.11 (1.3–3.5)	0.01	2.3 (1.3–4.1)	0.003
30–60	79	1.8	0.95 (0.7–1.3)	0.8	1.2 (0.8–1.7)	0.4
>60	38	1.5	0.76 (0.5–1.1)	0.2	1 (ref)	
CKD-EPI (ml/min x1.73 m^2)	136	1.8				
< 30	15	3.8	2.10 (1.2–3.7)	0.01	2.3 (1.3–4.2)	0.005
30–60	64	1.8	1.0 (0.7–1.4)	0.98	1.1 (0.8–1.6)	0.6
>60	57	1.6	0.79 (0.6–1.1)	0.2	1 (ref)	

RR, relative risk; CI, confidence interval; OR, odds ratio.

Table 5: Distribution of patients in relation to eGFR calculated by different formulas and agreement among formulas.

Formulas for eGFR (n. of patients)						
eGFR ml/1.73 m^2	C-G (2474*/4093)	MDRD (3169*/4093)	CKD-EPI (3169*/4093)	*k* CG vs. MDRD	*k* CG vs. CKD-EPI	*k* MDRD vs. CKD-EPI
<30	247 (10.0)	236 (7.4)	184 (5.8)	0.57	0.60	0.74
30–40	502 (20.3)	381 (12.0)	281 (8.9)			
40–50	747 (30.2)	444 (14.1)	389 (12.2)			
50–60	467 (18.8)	1052 (33.2)	818 (25.9)			
30–60	1716 (69.3)	1877 (59.3)	1488 (47.0)	0.30	0.39	0.62
>60	511 (20.7)	1056 (33.3)	1497 (47.2)	0.34	0.46	0.67

(*)n. of patients for whom all parameters for the calculation are available. n = number of patients.

prevalence dramatically increases with increasing age (29), since it is well known that GFR decreases progressively with age, with a reduction of 0.87 ml/min/1.73 m^2 (95% CI 0.64–1.1) for each additional year of age (30). The presence of severe CKD has been consistently reported as an independent risk factor for mortality (29) and for bleeding in previous studies (32, 33). For example, in the RIETE study, Monreal et al. (34) reported a significantly increased risk of fatal bleeding in the first three months after VTE in patients with severe CKD as compared to patients without severe CKD, with an OR of 5.0 (95% CI 2.0 to 12.0). For this reason, several bleeding risk stratification models include renal failure as risk factor for bleeding (6–8). A number of studies have compared some of these equations in specific patient populations. Melloni et al. (35) compared C-G and MDRD in non-ST segment elevation acute coronary syndromes patients, and reported important CKD disagreements in a substantial proportion of the patients, with age and gender being among the major determinants of disagreement. Gouin-Thibault et al. (16) also reported poor concordance between C-G and MDRD equations in a retrospective study on elderly hospitalised patients. Also in our study a poor agreement between C-G and MDRD and between C-G and CKD-EPI equations was found, in particular when differentiating patients with moderate CKD and patients with normal renal function. However, a better agreement among all equations was found for patients with severe CKD. As in previous studies, the use of the C-G formula resulted in an overestimation of the rate of patients with impaired renal function as compared to the use of either the MDRD or the CKD-EPI equations (36). Yet, the association between severe CKD and the occurrence of major bleeding events was similar regardless of the equation used. Similarly, eGFR<30 ml/min/1.73 m^2 is associated with an increased mortality regardless of the equation used (31).

Since patients receive VKA for long periods of time, frequently life-long, the progressive decline in renal function needs to be taken into account. Moreover, elderly patients are frequently prone to acute episodes of intercurrent diseases, such as infections or heart failure, which are commonly associated with a rapid worsening of the renal function. This issue will become even more relevant with the future use of the new oral anticoagulant drugs, such as the direct thrombin inhibitors and the direct factor Xa inhibitors, which, like heparins and unlike the VKA, are mainly cleared via the kidneys and tend to bioaccumulate in the presence of kidney failure.

In the analysis of other bleeding risk factors, we found that the history of bleeding, the presence of active cancer and the history of falls, are independently associated with bleeding.We also found a trend to a slight increase in bleeding rate among males. None of the other variables was an independent predictor of major haemorrhage. In particular, the bleeding risk was not associated with the quality of anticoagulation expressed as TTR, probably due to the elevated TTR of the whole population examined.

What is known about this topic?

- Vitamin K antagonists (VKA) are increasingly used in elderly for prevention of stroke in atrial fibrillation and for venous thromboembolism.
- Renal function progressively decreases with age and renal failure is frequent among elderly.
- Renal function is staged on the basis of estimated glomerular filtration rate (eGFR) and renal failure is associated with an increased risk for bleeding.

What does this paper add?

- Among ambulatory patients older than 80 years only a proportion ranging from 20.7 to 47.2% had a normal renal function and differences are due to the equation used to estimate the GFR.
- Although the different available equations yield different estimations of the severity of kidney disease, all equations appear to be similarly accurate to predict the risk of major bleeding in patients on VKA treatment.

Study limitations

A first potential limitation of our study is that we could not perform a direct measurement of the GFR, to be used as a referral standard. However, most of the studies published in the last years only relied on the available equations as surrogate markers of kidney

The following investigators and centres participated (no. of enrolled patients):

- Daniela Poli (chairman), Thrombosis Centre Department of Heart and Vessels, AOU-Careggi, Firenze (coordinating centre) (330)
- Sophie Testa, Oriana Paoletti, Haemostasis and Thrombosis Centre A O Istituti Ospitalieri di Cremona, Cremona (1,344)
- Giovanni Nante, Vittorio Pengo, Department of Medical and Surgical Science University of Padova (287)
- Umberto Carini, Cardiovascular Medicine, Misericordia Hospital Grosseto (280)
- Giuliana Guazzaloca, Gualtiero Palareti, Department of Angiology and Blood Coagulation "Marino Golinelli", University Hospital S. Orsola-Malpighi, Bologna (199)
- Anna Rita Scortechini, Lucia Canafoglia, Simona Tomassetti, Haematology Clinic Umberto 1° Hospital Ancona (183)
- Domenico Restifo, Thrombosis Centre AO Desio-Vimercate Vimercate (172)
- Antonio Ciampa, UOSS "Thrombosis Centre" AORN SG Moscati Avellino (142)
- Pasquale Pignatelli, Stefania Basili and Mirella Saliola Department of Experimental Medicine Sapienza University Roma (142)
- Leonardo Di Gennaro, Raimondo De Cristofaro, Haemostasis Research Center, School of Medicine Catholic University Roma (131)
- Walter Ageno, Monica Caprioli, Department of Clinical Medicine University of Insubria Varese (110)
- Simona Pedrini, Laboratory Service Istituto Ospedaliero Fondazione Poliambulanza Brescia (95)
- Francesco Orlandini, Raffaella Benedetti, Department of Internal Medicine 1, Civic Hospital S. Andrea, La Spezia (80)
- Lucia Rnocco, Thrombosis Centre Cisanello Hospital Pisa (74)
- Eros Tiraferri, Thrombosis Centre Civic Hospital Rimini (65)
- Roberto Cappelli, Thrombosis Centre AO Siena (62)
- Antonietta Piana, Ugo Armani, Department of Internal Medicine University of Genova, Genova (60)
- Alessandro Porcu, Thrombosis Centre ASL n° 8 Cagliari (57)
- Pietro Falco, Thrombosis Centre Hospice San Marco Latina (54)
- Paolo Da Col, Distretto n.1 Sanitary Service Regione Friuli Venezia Giulia Trieste (51)
- Francesco Marongiu; Doris Barcellona, Department of Medical Sciences "Mario Aresu" University of Cagliari, Cagliari (45)
- Anna Falanga, Teresa Lerede; Department of Oncology/Hematology Ospedali Riuniti Bergamo (39)
- Loreto Galbo, Laboratory Service Cervello Hospital Palermo (27)
- Eugenio Bucherini, Angiology Unit Civic Hospital Faenza (Ravenna) (26)
- Antonio Insana Department of Clinical Pathology, S. Croce Hospital, Moncalieri (TO) (16)
- Lucilla Masciocco, UOC Internal Medicine, Lastaria Hospital Lucera (FG) (14)
- Fabio Pini, Thrombosis Centre Civic Hospital "Villa Marina" Piombino (8)

disease and, thus, our results can well compare with the results of previous trials. Second, serum creatinine levels were measured by different laboratories. This might be a source of variability contributing to limit the agreement between formulas. However, all the laboratories complied with quality control programs, and the inter-laboratory variability for creatinine measurement is acceptably low among Italian laboratories. In addition, the body weight was available only for 60% of patients, limiting the applicability of C-G formula to this group of patients.

Finally, there was no independent adjudication committee for this study, therefore the definition of the study endpoints was based on the definitions provided by each participating centre. However, participating centres were required to clearly describe all adverse events and, for all events that lacked of adequate description in the data set, the coordinating Centre requested further information to ascertain the real occurrence of the event. When the event did not fulfil definition, it was not included.

Conclusions

In a population of elderly (age >80 years) patients receiving VKA, eGFR < 30 ml/min was associated with an increased rate of major haemorrhagic events. Because serum creatinine levels are inadequate for detecting CKD in the elderly, we suggest periodic monitoring of eGFR in elderly patients receiving VKA therapy. Although the different available equations yield different estimations of the severity of kidney disease, all equations appear to be similarly accurate to predict the risk of major bleeding in patients on VKA treatment.

Conflicts of interest

None declared.

References

1. Mant J, Hobbs FD, Fletcher K, et al.; Midland Research Practices Network (MidReC) Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007; 370: 493–503.
2. Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost 2011; 106: 739–749.
3. Douville P, Martel AR, Talbot J, et al. Impact of age on glomerular filtration estimates. Nephrol Dial Transplant 2009; 24: 97–103.
4. Pereira BJ. Introduction: new perspectives in chronic renal insufficiency. Am J Kidney Dis 2000; 36: S1–3.
5. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008; 117: e25–146.
6. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998; 105: 91–99.

7. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006; 151: 713–719.
8. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138: 1093–1100.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.
10. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010; 12: 1360–1342.
11. You JJ, Singer DE, Howard PA, et al. Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e531S-575S.
12. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease study group. Ann Intern Med 1999; 130: 461–470.
13. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247–254.
14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612.
15. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1–266.
16. Gouin-Thibault I, Pautas E, Mahé I, et al. Is Modification of Diet in Renal Disease formula similar to Cockcroft-Gault formula to assess renal function in elderly hospitalized patients treated with low-molecular-weight heparin? J Gerontol A Biol Sci Med Sci 2007; 62: 1300–1305.
17. Spruill WJ, Wade WE, Cobb HH 3rd. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. Clin Pharmacol Ther 2009; 86: 468–470.
18. Poli D, Antonucci E, Testa S, et al. Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. Circulation 2011; 124: 824–829.
19. Tripodi A, Chantarangkul V, Akkawat B, et al. A partial factor V deficiency in anticoagulated lyophilized plasmas has been identified as a cause of the international normalized ratio discrepancy in the external quality assessment scheme. Thromb Res 1995; 78: 283–292.
20. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2002; 26: S5–20.
21. Rosendaal FR, Cannegieter SC, van der Meer FJM, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69: 236–239.
22. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996; 348: 423–428.
23. Palareti G, Hirsh J, Legnani C, et al. Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. Arch Intern Med 2000; 160: 470–478.
24. Garcia DA, Lopes RD, Hylek EM. New-onset atrial fibrillation and warfarin initiation: high risk periods and implications for new antithrombotic drugs. Thromb Haemost 2010; 104: 1099–1105.
25. Duncan L, Heathcote J, Djurdjev O, et al. Screening for renal disease using serum creatinine: who are we missing? Nephrol Dial Transplant 2001; 16: 1042–1046.
26. Swedko PJ, Clark HD, Paramsothy K, et al. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003; 163: 356–360.
27. Rimon E, Kagansky N, Cojocaru L, et al. Can creatinine clearance be accurately predicted by formulae in octogenarian in-patients? QJM 2004; 97: 281–287.
28. Pedone C, Corsonello A, Incalzi RA; GIFA Investigators. Estimating renal function in older people: a comparison of three formulas. Age Ageing 2006; 35: 121–126.
29. Nygaard HA, Naik M, Ruths S, et al. Clinically important renal impairment in various groups of old persons. Scand J Prim Health Care 2004; 22: 152–156.
30. Michels WM, Grootendorst DC, Verduijn M, et al. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol 2010; 5: 1003–1009.
31. Corsonello A, Pedone C, Lattanzio F, et al. Chronic kidney disease and 1-year survival in elderly patients discharged from acute care hospitals: a comparison of three glomerular filtration rate equations. Nephrol Dial Transplant 2011; 26: 360–364.
32. Falga C, Capdevila JA, Soler S, et al. Clinical outcome of patients with venous thromboembolism and renal insufficiency: Findings from the RIETE registry. Thromb Haemost 2007; 98: 771–776.
33. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. Thromb Haemost 2011; 106: 997–1011.
34. Monreal M, Falgá C, Valle R, et al. Venous thromboembolism in patients with renal insufficiency: findings from the RIETE Registry. Am J Med 2006; 119: 1073–1079.
35. Melloni C, Peterson ED, Chen AY, et al. Cockcroft-Gault versus modification of diet in renal disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2008; 51: 991–996.
36. Roberts GW, Ibsen PM, Schiøler CT. Modified diet in renal disease method overestimates renal function in selected elderly patients. Age Ageing 2009; 38: 698–703.

