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Assessment of agreement and time in therapeutic range of capillary versus venous international normalised ratio in frail elderly people in a nursing home

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international normalised ratio, elderly, vitamin K antagonist, point-of-care testing, coagulometer.

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Abstract

Vitamin K antagonists are widely used, yet have a slim therapeutic margin and high iatrogenicity. Patients are monitored through international normalised ratio (INR) by venipuncture, but coagulometers could measure INR by capillary puncture. This prospective study evaluated the clinical concordance of capillary INR versus venous INR in 31 nursing home patients. Concordance was good and mean time in therapeutic range (TTR) markedly increased. Capillary INR is thus reliable, could improve TTR and decrease iatrogenicity.

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In France in 2011, 12% of subjects ≥75 years were treated with vitamin K antagonists (VKA) and 18.5% of those ≥85 years.[1] However, haemorrhage risk is high:

4.2% per year in patients >75 years,[2] therefore biological monitoring is essential. The index test is venous sampling of the international normalised ratio (INR) with a therapeutic target of 2.5 for most indications, including atrial fibrillation (AF) and deep venous thrombosis. The current recommendations are for monthly INR testing.[3] Time in therapeutic range (TTR) assesses the risk/benefit of treatment.[4] A 2013 study showed a mean TTR of 57.9% in French nursing home patients,[5] well below the threshold for a good risk/benefit ratio (65%).[6]

Poor venous access in elderly patients is a major obstacle to venous punctures and most INR sampling does not follow best practice, leading to inaccurate results.[7] Capillary INR monitoring is already described for patients[8,9] and in hospitals for commencing treatment[10] and for emergency management of stroke[11] with good numerical correlation. However, only one short-term correlation study has been performed in elderly patients, in a French geriatric hospital.[12] There are no published data on the agreement between venous and capillary INR for nursing home patients.

This study evaluated the agreement for clinical decision on the therapeutic adaptation between capillary and venous INR in nursing home patients. Secondary objectives were assessment of the TTR, the coefficient of variation of capillary INR per patient and the number of venous thromboembolic and haemorrhagic events. The hypothesis was that the agreement between capillary and venous INR is good.

This prospective pilot study was carried out in a nursing home between February and August 2016. The Institutional Review Board approved the study, which was designed according to STARD guidelines. All consenting patients treated with VKA for more than 6 months were included unless their participation was refused by their doctor.

Capillary INR was measured by trained nurses using the CoaguchekXS (Roche Diagnostics, Meylan, France), following the manufacturer's instructions, with the use of test strips, in the patients' room. Venous INR samples taken by nurses were analysed at the local biology laboratory, blinded to capillary result.

Capillary monitoring was performed weekly, with no venous INR verification if results were in the therapeutic range (1.9–3.1). Venous INR was performed when capillary INR was out of this range, and systematically monthly. In case of discordance, the treatment dose and the next scheduled capillary INR test date were adapted according to the venous INR result. If capillary INR >4, verification was made by venipuncture and the general practitioner intervened for management of overdose.

Initially, all discordances between monthly capillary and venous INR measurements were verified by venous INR 24 h later but this required excessive venipunctures, thus discordances ≤0.3 were recorded as discordant without further action. Only discordance >0.3 was verified by venous INR within 24 h, and in persistence of any degree of discordance, the INR was considered discordant.

Capillary INR was also measured upon: treatment with anti-inflammatory drugs, antiaggregating platelet, miconazole, or haemorrhagic signs (according to BARC classification[13]) or thrombosis. All samples from included patients were analysed, including patients leaving the study prematurely.

Quantitative data are expressed as mean ± standard deviation or median with interquartile range ((25th percentile − 75th percentile)) as appropriate. Qualitative variables are expressed as frequency with percentage. Clinical decision agreement was estimated by weighted kappa coefficient (κw; CI 95%): κw > 0.8 is considered excellent, >0.6 good, >0.4 average, >0.2 poor, >0 bad, and <0 inexistent. Clinical decision threshold was based on Haute Autorité de Santé (HAS) recommendations for target INR and overdose interventions <1.9, (1.9; 3.1), (3.1; 4), (4; 6), ≥6 (3).

Biological agreement was assessed by intra-class correlation coefficient (ICC; 95% CI). ICC is considered as excellent >0.9, acceptable >0.8, weak >0.6 and inexistent <0.6. Bias was measured by Bland–Altman plot, and discordance between clinical decisions following capillary and venous INR results was assessed by McNemar test. Intra-individual variability was estimated by coefficient of variation. TTR (NR 1.9–3.1) between strategies was tested using the Student paired test. Analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

No sample size evaluation was performed as this was a pilot study, and all patients treated with VKA at the nursing home could be included (potentially 40 patients).

Thirty-one nursing home residents (median age 89 years) were recruited from 1 February 2016 to 16 February 2016. Four residents dropped out (two from unrelated deaths and two from discontinuation of VKA due to hip fracture) (Supporting information, Figure 1). They were predominantly women treated for AF (Table 1).

Concordance calculated from 392 concomitant venous and capillary samples was good. The value of the lower bound of the 95% CI of the weighted kappa coefficient was 0.72 (κw = 0.76, 95% CI: (0.72; 0.81)). Agreement between venous and capillary INR value sampling was excellent (ICC = 0.93 with 95% CI (0.92; 0.94)). The McNemar test was significant ($P < 0.0001$). Of the 79 discordant concomitant measures, 63 (80%) corresponded to a venous INR in a higher clinical decision threshold. The Bland–Altman plot (Fig. 1) shows a mean difference between venous INR and capillary INR +0.12 (±0.28).

Historical TTR calculated from 173 samples from the 6 months preceding the study was 65% (95% CI (55%;

Table 1 Patient characteristics at inclusion

	n = 31
Female	25 (81%)
Age (years)	89 (84; 92)
BMI (kg/m^2)	25 (22; 28)
Systolic arterial pressure (mmHg)	134 ± 23
Diastolic arterial pressure (mmHg)	73 ± 11
Serum creatinine (μmol/L)	77.5 (60; 88)
Reason for introducing VKA	
AF alone (complete arrhythmia by atrial fibrillation)	23 (74%)
DVT (deep venous thrombosis)	3 (10%)
AF + DVT	5 (16%)
Type of VKA	
Fluindione	24 (77%)
Warfarin	5 (16%)
Acenocoumarol	2 (7%)
Comorbidities	
Heart failure	16 (52%)
Myocardial infarction	5 (16%)
Stroke	10 (32%)
History of anaemia or bleeding	4 (13%)
Karnofsky index (%)	
30	2 (6%)
40	13 (42%)
50	9 (29%)
60	7 (23%)
CHA2DS2VASc score	
3	1 (3%)
4	5 (16%)
5	12 (39%)
6	8 (26%)
7	4 (13%)
8	1 (3%)
HASBLED score	
<3	7 (23%)
≥3	24 (77%)

Figures are given as mean ± standard deviation or median (IQR), or number (percentage), as appropriate. AF, atrial fibrillation; DVT, deep venous thrombosis; VKA, vitamin K antagonists.

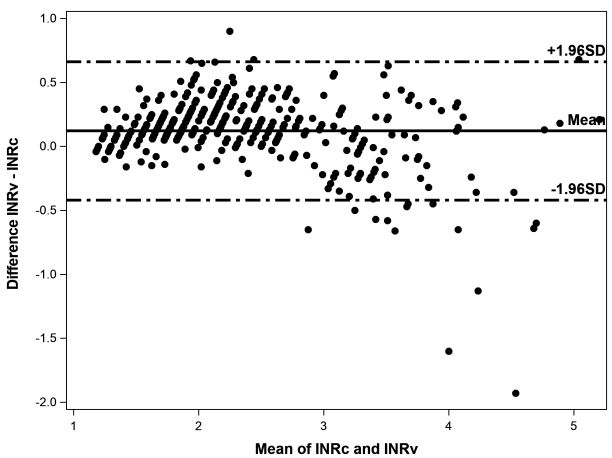

Figure 1 Bland–Altman plot.

75%)). The TTR calculated from the 894 capillary INRs during the study was 78% (95% CI (72%; 84%)); an average improvement in TTR of 13% (95% CI (3%; 23%)) (P = 0.0117). Patients >90 years (n = 17) had poorer historical TTR compared to patients <90 years (n = 14) (TTR 55 (42%; 67%) versus 73 (59%; 88%) respectively). Improvement of TTR in patients aged >90 years was greater than in younger patients, although not significant (20 (3%; 38%) versus 8 (5; 20)%, P = 0.2157).

The median individual coefficient of variation was 23% (18%; 34%). There were 12 type 1 haemorrhagic events and one suspected transitory ischaemic stroke, all in different patients, but no thromboembolic or other adverse events.

Discussion

Decision-making following capillary and venous INR results was good in elderly nursing home patients. In elderly patients, recommendations advise close monitoring of INR to improve VKA therapy management and decrease iatrogenicity.[14] Weekly capillary INR monitoring has since been adopted in this nursing home. Few studies are performed with frail elderly patients residing in nursing homes. Patients >90 years are rare in general population studies, yet accounted for almost half of the population here.

The frequent testing allowed analysis of a large number of samples, increasing the study power despite the small cohort. This is the largest study comparing capillary and venous INR samples in nursing home patients. The TTR estimate was reliable due to the length of the study and large number of samples analysed (n = 894). The historical TTR of patients at 65% was above the national average (57.9%)[5] yet significantly increased with weekly capillary monitoring. The largest disparities were between capillary INR (4–6) and venous INR (3.1–4). These thresholds prompt different interventions: for INR (3.1; 4), VKA dose is decreased; for INR (4; 6), VKAs are stopped until the INR returns to the target and then restarted at half dose. However, these cases represented less than half of all capillary INR (4–6) samples.

As a single-centre study, there is a possible selection bias. Nevertheless, patient characteristics are comparable to the population of elderly institutionalised patients.[5] A better end-point would be the number of thromboembolic and haemorrhagic events, but with a frequency of 3–5% in patients taking VKA, this would require too many patients. However, TTR is well correlated with these events. A 6.9% increase in TTR significantly reduces the risk of major haemorrhage (1/100 patient-years) and an 11.9% increase in TTR significantly reduces thrombotic risk (1/100 patients-years).[15]

We observed both a good decisional and numerical agreement between the capillary and venous INR. Excellent numerical agreement between methods has already been observed in a geriatric hospital (ICC = 0.97, $P < 0.0001$).[12] The results obtained in this previous study largely fell within the normal range, nevertheless, these results reinforced the reliability of capillary INR measurement.[16]

The advantages of capillary puncture monitoring are the speed and frequency possible.[16] Here, weekly monitoring of capillary INR significantly improved the TTR by 13%, sufficient to reduce the risk of iatrogenic accident (3/100 patient-year).[17] Increased TTR is associated with decreased mortality, myocardial infarction and stroke. Stroke prevention in patients with AF is effective when TTR is greater than 70%.[18] In the subgroup of patients >90, historical TTR was worse and improvement was greater. Thus, patients at highest risk for haemorrhage or thrombosis benefit most from capillary INR monitoring. We cannot yet determine whether the absence of serious haemorrhagic and thromboembolic events was due to the good TTR or the small sample size and short follow-up.

In 2018, the HAS recommended VKA or direct oral anticoagulants (DOA) as the first choice treatment in AF. DOA reduce the risk of haemorrhage without the constraint of regular venous monitoring. Yet their use is controversial: dabigatran, rivaroxaban and apixaban have only been evaluated in non-inferiority studies, and none show non-inferiority when TTR is >75%.[19] The 2016 European guidelines recommend VKA when the TTR is >70%.[20] In our study, the capillary TTR is 78%.

Nursing home patients are at risk of iatrongenic accidents from VKA. Decision-making between capillary and venous INR was good in these patients. Weekly capillary INR increased TTR and decreased VKA-related iatrogenism. The benefit of this strategy will now be tested in a national randomised cluster trial.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1. Patient flow-chart.

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The significance of anti-granulocyte-macrophage colony-stimulating factor antibodies in cryptococcal infection: case series and review of antibody testing

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autoantibody, *Cryptococcus*, cytokine, granulocyte-macrophage colony-stimulating factor, pulmonary alveolar proteinosis.

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Abstract

We report two cases of cryptococcosis, associated with anti-granulocyte-macrophage colony-stimulating factor antibodies. We review this recently identified acquired form of autoimmune immune deficiency and discuss the potential applications of granulocyte-macrophage colony-stimulating factor antibody testing by enzyme-linked immunosorbent assay.

A 48-year-old male firefighter presented with haemoptysis, 1 month after managing a bushfire. His medical history was notable for viral meningitis in adolescence, and nasal polyposis. Computed tomography (CT) chest imaging revealed a 25 mm right upper lobe cavitating mass extending

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