Letters to the editor

OVERVIEW

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Beware of thromboembolic risk in obese patients on direct oral anticoagulants (DOACs)

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Editor – We read with interest the article by Burden *et al* on pulmonary embolism in a patient on rivaroxaban and concurrent carbamazepine.[1] While the authors highlight the interaction between rivaroxaban and carbamazepine, one should be mindful of other risk factors that might reduce the therapeutic efficacy of a direct oral anticoagulant (DOAC), namely severe obesity, possibly due to suboptimal dosing regime in such patients.

We encountered an elderly woman with severe obesity (body weight: 120.95 kg, body mass index [BMI] 44 kg/m^2] who presented with pleuritic chest pain. She was taking apixaban 5 mg twice daily for atrial fibrillation. CT pulmonary angiogram confirmed an acute pulmonary embolus. There were no other risk factors and we felt that the reason for her suboptimal anticoagulation was severe obesity as this could have led to higher volume of distribution and lower mean peak concentration of apixaban.[2] We stopped the apixaban and treated her with warfarin.

Studies using DOACs have had fewer obese or morbidly obese patients and only a few had analysed the effect of weight on the pharmacokinetic and pharmacodynamic properties of DOACs. Results indicated that patients with higher body weights had lower peak concentrations, increased volume of distribution and shorter half-lives of DOACs.[3,4]

Although dose adjustment of DOACs in severely obese patients are still not recommended on the product literature, expert guidance suggests avoiding DOACs in patients with a BMI of >40 kg/m^2, or a weight of >120 kg.[4] If DOACs are used in such patients, they recommend checking drug-specific peak and trough levels and substituting it with a vitamin K antagonist if the levels are below the expected range, rather than adjusting the DOAC dose.[4]

It is important to raise awareness of clinicians on this matter as venous and arterial thromboembolic events while taking DOACs account for 3–5% of adverse events that are reported to the Medicines and Healthcare products Regulatory Agency (MHRA).[5] While there is a need for more data on the efficacy of DOACs on obese patients, we also need guidance on the most appropriate anticoagulation regime for patients who suffer a thromboembolic episode despite being on a DOAC. ■

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Which crystalloid? Does fluid choice influence patient outcomes in sepsis?

Editor – I read with interest the informative review by Tidswell and Singer regarding the definition, pathophysiology, diagnosis and management of sepsis.[1]

The article correctly highlights that the issue of fluid choice for patients with sepsis is a key dilemma for both researchers and clinicians. The authors suggest that there is little to recommend one crystalloid over another as first-line resuscitation fluid.

Two recent studies have added to the increasing body of evidence that balanced crystalloid solutions are associated with improved outcomes compared to 0.9% saline for all patients.[2,3] These support existing evidence focusing exclusively on patients with sepsis, indicating better outcomes in patients managed with balanced crystalloids.[4]

There are clear limitations to the available evidence and studies vary according to inclusion criteria, design and outcome measurement. Any treatment choice must take into account patient-specific factors such as serum potassium levels and further research is needed to facilitate informed clinical decision making. However, it would appear that currently the balance of evidence is tipping in favour of balanced crystalloids and against 0.9% saline as the optimal resuscitation fluid for most patients. ■

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Flu-related absence, a small proportion of all-cause sickness absence

Editor – The recent paper by Pereira *et al* on potential for improved sickness absence following influenza vaccination in healthcare workers is interesting.[1] We wonder whether the authors conclusions are valid based on the data in their study.

Annual population influenza infection rates are reported at between 5–20%.[2] On average each flu case takes 3 days absence.[2] Not all of influenza cases result in absence from work.[3] In an average influenza season the expected contribution from influenza on total sickness absence may be 0.1–0.3%.

The vaccine is ineffective against other influenza-like illness (ILI) that are not caused by influenza. Generally the vaccine does not exactly match circulating seasonal flu strains, and other factors affect vaccine response,[4] which is at best about 60% effective.[5] Therefore, the impact of the vaccine on improvement of sickness absence can only be between 0.05 to 0.15% (average 0.1%).

The data analysis in this paper does correspond with the effect modelling outlined above. The authors' conclusion that 'A 10% increase in vaccination would be associated with a 10% fall in sickness absence rate' seems misleading based on the proportion of total sickness absence that is due to flu. In an average flu season the total proportion of influenza-related sickness absence rate is likely to be of the order of only a proportion (0.1%) of the all-cause absence rate of 4.5%. It may be that the authors intended to say that a 10% increase in vaccination would lead to a 10% fall in sickness absence in relation to influenza, but not total absence.

It may be time to review the efficacy of healthcare worker influenza vaccination against the desired objectives of public health policy. To aim to vaccinate 100% of a mostly healthy population, of whom at most about 20% may become infected, with an imperfect vaccine to improve sickness absence by 0.1% in the average flu season, seems of marginal benefit. ■

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Response

We thank the authors for their interest in our paper.[1] We analysed data from 223 healthcare trusts covered ~800,000 staff in each of four influenza seasons from 2011. Higher influenza vaccination rates were associated with reduced total sickness absence rates ($\beta = -0.425$ [95% CI −0.658, −0.192], $p<0.001$). From this, an increase of 10% in influenza vaccine uptake, such as the one observed between the 2012–13 and 2013–14 influenza seasons, would be associated with a decrease in approximately 0.43 percentage points in the absolute sickness absence rate. Considering the average sickness absence rate was 4.5% across the four influenza seasons. This reduction of 0.43 percentage points translates into a 10% relative decrease in the sickness rate, which suggests that increasing vaccine uptake can have a significant practical impact.

The most likely explanation for this is a direct effect of vaccination. A causal effect of vaccination is supported by the observation that the association between vaccination and sickness absence was only present during the flu season. In addition, the association was independent of staff satisfaction, so the explanation that a 'happy' workplace might lead independently both to higher vaccination rates and lower sickness absence cannot explain it.

Around 40% of NHS staff sickness absence is related to respiratory illness[2] and rates of healthcare worker (HCW) influenza infection are higher[3] than the range modelled in a general population.[4] Median duration of HCW sickness absence with flu is 4 days.[3] A significant proportion of HCWs have subclinical, but potentially transmissible, illness. The latter point means that the effect of vaccination will extend considerably beyond the individuals vaccinated, being multiplied by the reduction in transmission rates within the hospital environment and at home – vaccinated healthcare staff are therefore protecting their fellow workers as well as their patients,[5–9] their families and themselves.