Previously described mechanisms of abnormal coagulation studies in plasma cell dyscrasias include monoclonal protein interference with fibrin polymerisation⁸ and less commonly auto-antibody behaviour targeting specific proteins^{9,10} or heparin-like activity.^{5,11,12} AL amyloidosis may also be associated with Factor X deficiency, attributed to adsorption of Factor X to the amyloid fibrils. The mechanism of inhibition of multiple intrinsic factors in our cohort is unclear. The difference in bleeding phenotype between the three patients may be explained by the pattern of factor inhibition. The first patient had predominant inhibition of Factor XI and did not demonstrate a bleeding phenotype, while the other two patients, who did have bleeding complications following surgical procedures, had inhibition of multiple factors, most profound in the second patient.

Our case series suggests that patients with an incidental finding of prolonged APTT that does not correct on mixing should be evaluated for the presence of a paraprotein. However, the prolonged APTT may not predict bleeding phenotype. None of our patients have received treatment for their plasma cell dyscrasias or lymphoproliferative disorders thus far, and so it is not possible to evaluate whether their coagulation study abnormalities would improve with reduction in their paraprotein. Prospective evaluation of coagulation profiles in patients with newly diagnosed MGUS could provide epidemiological data regarding the prevalence of abnormal coagulation profiles in these patients.

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A case report of successful transition from argatroban to warfarin using DOAC-stop in heparin induced thrombocytopenia (HIT)

Sir,

Heparin induced thrombocytopenia (HIT) is a serious life-threatening complication due to exposure to heparin or low molecular weight heparin that necessitates anticoagulation with an alternative agent. A commonly used agent is argatroban, a direct thrombin inhibitor (DTI) which is safe to use in patients with concomitant renal failure. At some point there needs to be a switch from the argatroban infusion to an oral agent such as warfarin if direct oral anticoagulants (DOACs) are contra-indicated. The conversion from argatroban to warfarin can be difficult and there are no clear guidelines for this transition. The largest study of argatroban use in HIT, where 418 patients were treated and 63% were transitioned to warfarin, did not define the transition protocol or guideline used.¹

There are published suggestions on argatroban to warfarin transition used by different haematology centres. The most common method involves co-administration of argatroban and warfarin for 5 days, cessation of argatroban when the INR >4, repeat INR after 4 hours to ensure the warfarin is effective with a target INR of 2–3 and cessation of argatroban if this has occurred. If this has not occurred, the argatroban is re-commenced and these steps are repeated.²

An analysis of outcomes of patients who underwent an argatroban to warfarin transition as mentioned above was carried out by Bartholomew *et al.*³ They identified 111 patients who achieved an INR >4 during combined argatroban and warfarin therapy. Adverse outcomes occurred in nine (8.1%) patients during co-therapy and 12 (10.8%) patients after argatroban was discontinued, including seven new thrombosis, 12 deaths (11/12 died due to causes other than thrombosis) and one major bleed. Their conclusion was that in patients receiving argatroban/warfarin co-therapy and an INR >4, the risk of thrombosis exceeds the risk of bleeding. These data suggest that the traditional method of ceasing argatroban to check the warfarin induced change in INR in a population of patients already at high risk of thrombosis may not be an ideal method.

We report a case of argatroban to warfarin transition using DOAC-Stop, a commercial product that removes all types of DOACs (dabigatran, apixaban, rivaroxaban and edoxaban) from plasmas. Whilst DOAC-Stop has been used in the laboratory to overcome DOACs to good effect, this is the first described case of using DOAC-Stop to neutralise the effects of argatroban.^{4,5}

Fig. 1 Patient results during treatment (days 1–15).

A 75-year-old man presented to hospital with anuria due to bilateral renal artery stent thrombosis. He had a background of type 2 diabetes, ischaemic heart disease, abdominal aortic aneurysm with prior elective endovascular repair, stroke, atrial fibrillation on warfarin, congestive cardiac failure, chronic obstructive pulmonary disease and benign prostatic hypertrophy. The renal artery stent occlusion was precipitated due to premature patient initiated cessation of dual antiplatelets, in conjunction with active smoking.

He was managed by the vascular surgery team and treated with thrombolysis and a heparin infusion. His blood tests on admission showed a creatinine of 447 $\mu\text{mol/L}$, eGFR 10 mL/min/1.73 m², potassium 3.5 mmol/L, haemoglobin 129 g/L, platelets $167 \times 10^9/L$ and white cell count $12.6 \times 10^9/L$. His coagulation studies showed, prothrombin time (PT) of 18 s (normal range 11–16 s), international normalised ratio (INR) of 1.2, and activated partial thromboplastin time (APTT) of 39 s (range 24–36 s). He was noted to have a normal APTT of 30 s on recent previous testing. In our laboratory we use the NeoPTimal and Actin FS reagents for PT and APTT testing, respectively.

During the admission, his platelet count dropped to a nadir of $51 \times 10^9/L$ on day 4 after heparin exposure. His 4T HIT score was 4 (intermediate, 14% probability of HIT) based on timing and nadir of the drop. A HIT antibody screen was performed and Ig heparin dependent platelet antibody was detected at 7.03 U/mL (Acustar). Given the patient's renal failure the heparin was ceased and argatroban commenced. At this time the PT was 17 s, INR 1.2 and APTT 69 s. The argatroban was to be titrated using our standard hospital protocol with a target APTT of 1.5–3.0 $\times$ normal.

After initiation of argatroban, the PT was 27 s, INR 2.0 and APTT 88 s. We tested this same sample with DOAC-Stop as

per the manufacturer's instructions. The PT corrected to 15.9 s, INR 1.1 and APTT 37.2 s (Fig. 1). By day 5 on argatroban, the platelet count had risen to $114 \times 10^9/L$ and warfarin (5 mg daily) was commenced. Prior to warfarin commencement, the PT was 21 s, INR 1.5 and APTT 71 s. Three days later with argatroban and warfarin co-therapy, the INR was 2.9 and after DOAC-Stop the INR was 2.2. On day 4 of co-therapy, the INR was 5.1 and after DOAC-Stop, the INR was 3.5. Factor levels were checked on this day to ensure the INR was a reflection of depletion of the vitamin K dependent factors: FVII 7%, FIX 39%, FX 43%, FII 55%, FV 86% and FVIII 198%.

The argatroban infusion was stopped and warfarin continued and titrated as per normal. Our patient did not have any bleeding or clinical thrombotic complication during argatroban and warfarin co-administration or thereafter. His renal function improved with fluid management and conservative measures, creatinine 227 $\mu\text{mol/L}$, eGFR 23 mL/min/1.73 m² and he remains on warfarin therapy. A serotonin release assay was not performed to confirm the HIT antibody result.

HIT is not an uncommon clinical scenario and is often treated with argatroban especially in the setting of renal failure. In this situation there may be a need to transition a patient from argatroban to warfarin. Current methods of transitioning involve turning the infusion on and off with repeat INR checks. In a hospital setting this method has been shown to have a high rate of adverse events. We were able to successfully transition a patient from argatroban to warfarin using DOAC-Stop to neutralise the effect of argatroban during co-administration with warfarin. This appears to be an easy and safe method for argatroban to warfarin transition that warrants further investigation.

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A distinctive staining pattern with anti-3-hydroxy-3-methyl-glutaryl-coenzyme a reductase (HMGCR) antibodies on mouse kidney

Sir,

We report a distinctive indirect immunofluorescence staining pattern on mouse kidney with autoantibodies to anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR). The specificity of this staining pattern was confirmed using immunoabsorption experiments. The staining pattern was an incidental finding observed when testing a sample for tissue autoantibodies by immunofluorescence. The pattern may not have utility for routine immunofluorescence screening; however, it should prompt a HMGCR confirmatory test when observed.

In 2010, a link between necrotising myopathy and HMGCR autoantibodies was established.¹ The gold standard test for necrotising myositis confirmation is biopsy. However, the presence of HMGCR autoantibodies may be confirmed using radio-immunoprecipitation or counter-current immunoelectrophoresis (CIEP)^{2,3} to precipitate HMGCR recombinant protein. Automation of laboratory techniques has led to a reduction in labour intensive methods such as radio immunoprecipitation and/or CIEP. The importance of the immunoprecipitation assays is that they precipitate higher affinity antibodies that are considered more clinically relevant than those detected on screening tests such as enzyme-linked immunosorbent assay (ELISA). Thus, it is recommended that ELISA are used to screen samples when the pretest probability of anti-HMGCR myopathy is high in those with

significant creatinine kinase (CK) elevations and muscle weakness.⁴ A unique immunofluorescence pattern has also been described as a confirmatory/screening test. On rat liver, a scattered cytoplasmic staining of hepatocytes around the liver lobules, namely anti-HMGCR antibody associated liver immunofluorescence pattern (HALIP) is described.⁵

Our experience has found that of all samples sent for myositis testing, anti-HMGCR autoantibodies make up a third of those positive for a known myositis antibody, making it the most common form of myositis.³ The availability of anti-HMGCR positive samples by both ELISA and CIEP within our laboratory led to the identification of a distinctive immunofluorescence staining pattern on mouse kidney. The anti-HMGCR antibodies stain the distal kidney tubules which appear as distinct bands in the kidney. Mouse HMGCR is moderately expressed in kidney tissue (<http://www.informatics.jax.org/marker/MGI:96159>) and experimental nephropathy increases mouse renal HMGCR expression.⁶ We confirmed the specificity of the mouse kidney staining pattern to HMGCR using immunoabsorption experiments.

A 74-year-old female presented to her general practitioner with non-specific malaise, profound muscle weakness and decreased energy. Despite being a keen golfer, she was struggling to walk the golf course. Muscle pain, shortness of breath and intermittent palpitations were also recorded. She was known to have thyroid disease (Hashimoto's thyroiditis) and low B12 concentration. She had been taking the statin, atorvastatin, for 8 years. Tests for parietal cell and intrinsic factor autoantibodies were requested. Gastric parietal cell (GPC) antibodies were detected using indirect immunofluorescence (IIF) on ready made slides with mouse kidney and stomach (MKS) sections (Inova Diagnostics, USA) and patient serum at 1 in 20 dilution in phosphate buffered saline. In addition to the strong classical GPC pattern, an unusual pattern was observed in the distal kidney (Fig. 1A). This pattern was previously observed on IIF using murine tissue substrate from a patient with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) antibody positive necrotising myositis (Fig. 1B,C). When the patient's sample was tested for anti-HMGCR antibodies on our in-house ELISA it was strongly positive, 38 AU (arbitrary units; reference range 0–3) which was confirmed with immunoprecipitation to HMGCR on CIEP. CK was subsequently found to be elevated at 16,432 U/L (female reference range 30–180 U/L). The myositis line blot (Euroimmun, Germany) was negative for other myositis-associated autoantibodies (Mi-2 α , Mi-2 β , TIF1 γ , MDA5, NXP2, SAE1, Ku, PM-Scl 75, PM-Scl 100, Jo-1, SRP, PL-7, PL-12, EJ, OJ and Ro-52). The patient was commenced on prednisone and methotrexate for presumed autoimmune necrotising myositis. Regular atorvastatin was stopped, and clinical improvement was observed following initiation of immunosuppressive therapy. No muscle biopsy was undertaken.

Immunoabsorption experiments confirmed the pattern specificity. Using a strong positive anti-HMGCR sample at 1 in 20 dilution it was pre-incubated with 16, 4 and 1 μ g/mL of HMGCR antigen (Sigma, USA) prior to loading onto the mouse tissue slides. The strong distal kidney staining observed progressively diminished with increasing amounts of HMGCR added; staining at 1 μ g/mL was moderate-strong, reducing to weak at 4 μ g/mL and marginal at 16 μ g/mL. As further evidence, eight confirmed HMGCR positive samples