Vitamin D Therapy to Reduce Blood Pressure and Left Ventricular Hypertrophy in Resistant Hypertension

Randomized, Controlled Trial

Miles D. Witham, Sheila Ireland, J. Graeme Houston, Stephen J. Gandy, Shelley Waugh, Thomas M. MacDonald, Isla S. Mackenzie, Allan D. Struthers

Key Words: blood pressure • hypertension resistant to conventional therapy • vitamin D

Abstract—Low 25-hydroxyvitamin D levels are associated with higher prevalent blood pressure. We tested whether high-dose intermittent oral vitamin D therapy could reduce blood pressure and left ventricular mass in patients with hypertension resistant to conventional treatment. We conducted a parallel-group, double-blind, randomized placebo-controlled trial. Patients with supine office blood pressure >140/90 mm Hg on ≥3 antihypertensive agents received 100,000 U oral vitamin D3 or matching placebo every 2 months. Office and 24-hour ambulatory blood pressure, glucose, and cholesterol were measured at baseline, 2, 4, and 6 months; left ventricular mass index was measured by cardiac MRI on a subgroup at baseline and 6 months. The primary outcome was mean 24-hour ambulatory blood pressure at 6 months. A total of 68 participants were randomized, 34 in each group. Mean age was 63 (SD 11) years, mean baseline office blood pressure was 154/84 (13/10) mm Hg, and mean baseline 25-hydroxyvitamin D level was 42 (16) nmol/L. Treatment with vitamin D did not reduce 24-hour ambulatory blood pressure (adjusted treatment effects: systolic, +3 mm Hg; 95% confidence interval, −4 to +11; P=0.33; diastolic, −2 mm Hg; 95% confidence interval, −6 to +2; P=0.29); similar results were seen for office blood pressure. Left ventricular mass index was measured in a subgroup (n=25); no reduction was seen with vitamin D treatment (adjusted treatment effect, +4 g/m²; 95% confidence interval, 0 to +7; P=0.04). There was no significant change in cholesterol or glucose levels. Thus, 6 months of intermittent, high-dose oral vitamin D3 did not reduce blood pressure or left ventricular mass in patients with resistant hypertension. (Hypertension. 2014;63:706-712.) • Online Data Supplement

Randomized Hypertension Treatment (VITAL) Investigators. Randomized, Controlled Trial

Resistant hypertension, defined as an office systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg, despite maximally tolerated treatment with ≥3 antihypertensive agents, affects 10% to 30% of patients with hypertension. Resistance to treatment is associated with a high incidence of cardiovascular events. Resistant hypertension is also associated with a high incidence of left ventricular (LV) hypertrophy, itself a risk factor for cardiovascular events, arrhythmias, and death.

Relatively few studies target resistant hypertensive patients as a discrete subgroup, and treatment algorithms are not as well defined for this group of patients as for those with more straightforward mild to moderate hypertension. Despite a wide range of antihypertensive agents now available with multiple modes of action, treatment of resistant hypertension remains problematic, with many patients experiencing treatment-limiting side effects. Although recent interest has focused on invasive solutions, such as renal denervation therapy, the large burden of resistant hypertension at the population level means that inexpensive, easily applied interventions to mitigate the problem are still required.

Low vitamin D levels are associated with higher blood pressure and a higher rate of both incident hypertension and cardiovascular disease in observational studies. Previous intervention trials have suggested that vitamin D may reduce blood pressure in selected groups of patients with hypertension; however, no trials to date have evaluated the effects of vitamin D on resistant hypertension. Pathophysiological investigation suggests a link between low vitamin D levels and LV hypertrophy, possibly mediated by parathyroid hormone, but few studies have examined the effect of vitamin D analogues on LV mass. Therefore, we conducted a randomized controlled trial to test the effect of intermittent high-dose vitamin D on...
24-hour ambulatory blood pressure and LV mass in patients with resistant hypertension.

Methods

Design and Participants
We performed a randomized, double-blind, placebo-controlled, parallel-group trial. Participants were recruited via cardiovascular medicine clinics and via primary care services in Tayside, Scotland. Participants were eligible for inclusion if they were aged ≥18 years, had a supine office blood pressure of >140/90 mmHg, were on ≥3 antihypertensive medications (resistant hypertension), and had serum 25-hydroxyvitamin D (25OHD) levels <75 nmol/L.

Participants were excluded if they had hypertension known to be caused by a correctable underlying surgical or medical cause and had albumin-adjusted calcium levels of >2.60 or <2.15 mmol/L, sarcoidosis, history of renal stones, or a previous clinical diagnosis of osteomalacia. Other exclusion criteria were liver function tests >3× upper limit of normal, estimated glomerular filtration rate by the Modified Diet in Renal Disease for variable equation of <40 mL/min, metastatic malignancy, heart failure with LV systolic dysfunction, or known atrial fibrillation. Participants were excluded if already taking pharmacological vitamin D preparations (fish oils were permitted), were unable to give written informed consent, were pregnant and lactating, or were women of childbearing age without taking reliable contraception. Participants with contraindications to MRI scanning were permitted to enter the main study but were excluded from the MRI substudy. Written informed consent was obtained from all participants; ethical approval was given by Tayside Research Ethics committee (ref: 08/IS1402/31). Clinical trials authorization was obtained from the UK Medicines and Healthcare Regulatory Authority (EdRAcT ref: 2008-002681-63), and the trial was prospectively registered with www.controlled-trials.com (ISRCTN63688695).

All participants gave written informed consent, and the trial conformed to the principles of the Declaration of Helsinki.

Intervention
After completion of all baseline measurements including MRI if performed, participants were allocated the next sequentially numbered treatment pack. Packs contained either vitamin D3 (Vigantol oil; donated by Merck Serono KgAA) or identical placebo oil (Mygliol oil, used as the base oil for Vigantol). Medications were overlabeled and prepared by Tayside Pharmaceuticals (Dundee, United Kingdom) and were supplied in identical bottles with study number but no indication of group allocation. Therefore, allocation was concealed from researchers and participants. After completion of assessments, a 5-mL dose was administrated by the study nurse at baseline, 2 months, and 4 months to ensure 100% adherence. Therefore, the total dose administered was 300,000 U of vitamin D3 or placebo. All prestudy antihypertensive medications were continued.

Outcome Measures
Outcomes were performed at 0, 2, 4, and 6 months by a research nurse blinded to study allocation. The primary outcome was between-group difference in mean 24-hour ambulatory systolic blood pressure at 6 months.

Twenty-four-hour blood pressure was measured using Meditech ABPM-04 ambulatory blood pressure monitors and analyzed using Cardiovisions data analysis software. Blood pressure was measured as the area under the curve of 30 seconds minimum of every 30 minutes during the day (0600-2200 hours) and a minimum of every 60 minutes overnight (2200-0600 hours). The mean of the total 24-hour readings was used as the primary outcome measure. Office blood pressure was measured in the supine position after 5 minutes of rest using an OMRON HEM-705CP automated blood pressure cuff. Three consecutive readings were taken; the mean of the second and third readings was taken as the outcome measure. Fasting blood was drawn for measuring 25OHD, which was measured using the IDS radioimmunoassay (coefficient of variation, 6.3%). Calcium, parathyroid hormone, creatinine, glucose, and total cholesterol were measured according to standard protocols in the Department of Biochemical Medicine, NHS Tayside, Dundee, United Kingdom.

Cardiac MRI
Cardiac MRI was performed using a 3 Tesla Magnetom Trio scanner (Siemens, Erlangen, Germany). After initial standard localization sequences, a series of 6-mm short-axis (55° flip angle) 2-dimensional segmented cine ECG-gated breath-hold steady-state free precession (TrueFISP) images was acquired from the base to apex of the LV to enable measurement of LV mass and wall thicknesses. Postprocessing delineation of epicardial and endocardial borders (at end-diastole and end-systole) was performed using commercial cardiac evaluation software (Argus VB17; Siemens) by an experienced MRI physicist who was blind to the treatment allocation and not otherwise involved with the running of the study. Papillary muscles and trabeculae were routinely assigned to the LV blood pool if they were identified as structurally distinct from the myocardial wall but otherwise assigned to the myocardial mass. Only those image slices that displayed >50% full-thickness myocardium were analyzed. All data sets were evaluated twice for a time-course of 1 month to establish a mean (and corresponding repeatability evaluation) for the quantitative MRI parameters without the inclusion of segmentation learning effects. LV mass index was calculated by dividing LV mass by body surface area, calculated as the square root of 

\[ \sqrt{\text{weight in kg} \times \text{height in cm}/3600} \]

For measurement of left atrial end-diastolic volume, 5-mm multislice vertical long axis 2-chamber images were acquired from the lateral side of the left atrium to the atrial septum perpendicular to the plane of the mitral valve. The volume at atrial end-diastole contained by the atrial wall and the clearly delineated mitral valve was calculated. The left atrial appendage was included in the atrial volume measurements, and pulmonary vein structure was excluded wherever possible.

Asymptomatic hypercalcemia (>2.60 mmol/L) was recorded as a prespecified adverse outcome, and no further doses of study medication were administered if this occurred. All adverse events were recorded at each study visit along with information on medication use and comorbidity disease.

Statistical Analysis
The trial was powered for an 8-mmHg fall in systolic blood pressure, based on data from previous trials using similar doses of vitamin D. Assuming a SD of change of 11 mmHg, 31 patients per group (62 in total) would be required to detect this change with 80% power at α=0.05. To achieve this final evaluable sample size of 62 participants, we originally aimed to recruit a total of 74 patients to allow for a dropout rate of 20%, based on previous similar studies in our department. For LV mass index, a change of 10 g is regarded as clinically significant, and a total of 26 to 30 subjects is required to demonstrate a 10 g change with 90% power at α=0.05.

Analyses were performed using SPSS version 18 (SPSS, Chicago, IL). Comparisons between continuous variables were performed using Pearson χ² or using Fisher exact test when the contents of any cell was ≤5. Repeated measures ANOVA was also undertaken to estimate the overall treatment effect using all available data for outcomes with >2 timepoints; for cardiac MRI, ANOVA was used to compare 6-month values between groups, adjusting for baseline values. Multiple imputation was used to address missing data for the primary outcome; 5 imputations were performed, using baseline and follow-up blood pressure data, baseline age, sex, and 25OHD level to generate imputed data sets. A sensitivity analysis was performed, excluding participants who changed their antihypertensive medication for the 6-month study period. A 2-sided P value of 0.05 was taken as significant for all analyses.

Results
Details of participant flow through the trial are given in the Figure. A total of 68 participants met the inclusion and exclusion criteria and were randomized into the study.
Randomization took place between January 2009 and February 2011. Baseline details for the 68 subjects randomized into the trial are shown in Table 1. All participants were of white ethnic background. A total of 61/68 (90%) participants underwent the 6-month visit. Recruitment was terminated before the target number of participants was reached, in part, because of slow recruitment rates and, in part, because of the lower than anticipated dropout rate.

Table 2 shows the effect of the intervention on the 24-hour blood pressure and office blood pressure. No significant improvement in either 24-hour blood pressure or office blood pressure was seen with vitamin D supplementation at any time-point; indeed the repeated measures analysis suggested a non-significant increase in blood pressure in the treatment group. Sensitivity analysis was performed using multiple imputation to address missing data for the primary outcome. The treatment effect for 24-hour ambulatory systolic blood pressure remained nonsignificant (+1 mmHg; 95% confidence interval [CI], –3 to +5), and the effect for 24-hour ambulatory diastolic blood pressure was of borderline significance (–3 mmHg; 95% CI, –6 to 0). A further sensitivity analysis was performed excluding the 9 participants (4 in vitamin D group and 5 in placebo group) who changed antihypertensive medication during the trial. In this analysis, little difference was seen in the results for 24-hour blood pressure (repeated measures systolic treatment effect, 3 mmHg; 95% CI, –4 to 11; P=0.38 and diastolic treatment effect, 2 mmHg; 95% CI, –6 to 9; P=0.67) or for office blood pressure (repeated measures systolic treatment effect, 3 mmHg; 95% CI, –4 to 10; P=0.38 and diastolic treatment effect, –3 mmHg; 95% CI, –8 to 2; P=0.30).

Adjusted repeated measures analysis of daytime ambulatory blood pressure change showed no effect of vitamin D (systolic treatment effect, +1 mmHg; 95% CI, –6 to 9 and diastolic treatment effect, –3 mmHg; 95% CI, –7 to +1); similarly, analysis of night-time ambulatory blood pressure change showed no significant treatment effect (systolic treatment
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effect, +4 mm Hg; 95% CI, –3 to +12 and diastolic treatment effect, –1 mm Hg; 95% CI, –6 to +3).

Table 3 shows the results of the cardiac MRI substudy. A total of 37 patients progressed to MRI scanning at baseline; 8 participants did not complete baseline MRI scans successfully because of breathlessness (2 participants), claustrophobia (3 participants), and failure to fit into the scanner (3 participants). Therefore, a total of 29 patients underwent successful baseline MRI scanning; 25 underwent follow-up scans at 6 months (11 in the treatment arm and 14 in the placebo arm). Left atrial images of sufficient quality for volumetric analysis at both baseline and follow-up were available for 15 participants. Baseline end-diastolic volume and LV mass index were nonsignificantly lower in the vitamin D group. No difference in ejection fraction, LV end-diastolic volume, or left atrial end-diastolic volume was seen with treatment; LV mass index increased slightly with treatment, with this change reaching significance after adjustment for baseline blood pressure and 25OHD level.

Similar numbers of adverse events were noted in each group; 35 in the active treatment arm and 38 in the placebo group. No participant died during trial participation; 1 participant had a cardiovascular event in the active treatment group (angina) not requiring hospitalization, and 1 had a cardiovascular event in the placebo group (myocardial infarction) requiring hospitalization. No participant had serum calcium >2.60 mmol/L at any timepoint. Details of adverse events are given in Table S1 in the online-only Data Supplement.

Discussion

This study failed to show any effect of high-dose, intermittent vitamin D supplementation on blood pressure, cholesterol, glucose, or LV mass measured using cardiac MRI. This was despite the administration of relatively high doses of oral
vitamin D (equivalent to 1800 U/d), with a substantial and sustained rise in 25OHD levels in the treatment group.

Several possibilities merit discussion to explain our findings. It is possible that the dose of vitamin D was insufficient to produce the required biological effect. Previous studies using similar doses in selected patients groups (eg, those with type 2 diabetes mellitus) have, however, shown significant reductions in blood pressure; these studies included a proportion of patients with suboptimally treated hypertension.17,18 Although the 25OHD levels fell short of the 75nmol/L level claimed by some commentators to be necessary for optimum health,20 no evidence exists to support a threshold effect of 25OHD level to produce beneficial vascular effects. Similarly, although the study was only of 6-month duration, reductions in blood pressure in previous studies have been seen within a few weeks of large oral doses of vitamin D. Reduction in LV mass on MRI has been demonstrated within 9 months with other vascular interventions, for instance by previous studies on allopurinol and on blood pressure reduction.21,22 However, our results are consistent with the main findings of

Table 2. Effect of Vitamin D Supplementation on Mean 24-Hour Ambulatory Blood Pressure and Office Blood Pressure

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Systolic BP, mm Hg (SD)</th>
<th>Diastolic BP, mm Hg (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vitamin D</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>138 (18)</td>
<td>137 (13)</td>
</tr>
<tr>
<td>2 mo</td>
<td>136 (15)</td>
<td>134 (13)</td>
</tr>
<tr>
<td>4 mo</td>
<td>137 (17)</td>
<td>130 (9)</td>
</tr>
<tr>
<td>6 mo</td>
<td>136 (14)</td>
<td>130 (14)</td>
</tr>
<tr>
<td>Unadjusted RM* (95% CI)</td>
<td>4 (~3 to 11)</td>
<td>0.20</td>
</tr>
<tr>
<td>Adjusted RM† (95% CI)</td>
<td>3 (~4 to 11)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Office blood pressure

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Active (n=11)</th>
<th>Placebo (n=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>153 (11)</td>
<td>155 (14)</td>
<td>0.51</td>
</tr>
<tr>
<td>2 mo</td>
<td>154 (18)</td>
<td>150 (12)</td>
<td>0.40</td>
</tr>
<tr>
<td>4 mo</td>
<td>152 (14)</td>
<td>147 (13)</td>
<td>0.21</td>
</tr>
<tr>
<td>6 mo</td>
<td>151 (19)</td>
<td>146 (16)</td>
<td>0.35</td>
</tr>
<tr>
<td>Unadjusted RM* (95% CI)</td>
<td>4 (~2 to 10)</td>
<td>0.24</td>
<td>~3 (~7 to 1)</td>
</tr>
<tr>
<td>Adjusted RM† (95% CI)</td>
<td>4 (~3 to 10)</td>
<td>0.25</td>
<td>~3 (~7 to 1)</td>
</tr>
</tbody>
</table>

25OHD indicates 25-hydroxyvitamin D; BP, blood pressure; CI, confidence interval; and RM, repeated measures.
*Repeated measures treatment effect.
†Adjusted for baseline 25OHD level.

Table 3. Cardiac MRI Measures

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Active (n=11)</th>
<th>Placebo (n=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>72.3 (6.0)</td>
<td>71.5 (6.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>6 mo</td>
<td>70.6 (3.7)</td>
<td>70.0 (8.1)</td>
<td>0.79</td>
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<tr>
<td>Unadjusted treatment effect (95% CI)</td>
<td>0.2 (~4.7 to 5.2)</td>
<td>0.92</td>
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<tr>
<td>Adjusted† treatment effect (95% CI)</td>
<td>2 (~3.1 to 7.1)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Baseline LVMI, g/m² (SD)</td>
<td>57 (13)</td>
<td>62 (16)</td>
<td>0.58</td>
</tr>
<tr>
<td>6 mo LVMI, g/m² (SD)</td>
<td>58 (13)</td>
<td>61 (16)</td>
<td>0.58</td>
</tr>
<tr>
<td>Unadjusted treatment effect (95% CI)</td>
<td>2 (~1 to 5)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Adjusted† treatment effect (95% CI)</td>
<td>4 (~0 to 7)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Baseline LVEDV, cm³ (SD)</td>
<td>140 (32)</td>
<td>155 (26)</td>
<td>0.21</td>
</tr>
<tr>
<td>6 mo LVEDV, cm³ (SD)</td>
<td>136 (26)</td>
<td>154 (41)</td>
<td>0.22</td>
</tr>
<tr>
<td>Unadjusted treatment effect (95% CI)</td>
<td>~3 (~22 to 16)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Adjusted† treatment effect (95% CI)</td>
<td>~8 (~29 to 13)</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EF, ejection fraction; LAEDV, left atrial end-diastolic volume; LVEDV, left ventricular end-diastolic volume; and LVMI, left ventricular mass index.
*Adjusted for baseline systolic blood pressure and 25-hydroxyvitamin D level.
the PRIMO (Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity) trial, which showed no effect of 48 weeks of paricalcitol therapy on LV mass in patients with advanced kidney disease.14 Changes in left atrial volume may provide a more sensitive early measure of cardiac remodeling, and a substudy of PRIMO did find a reduction in left atrial volume with paricalcitol therapy23; we were unable to demonstrate this in the current study although the number of patients with usable left atrial volumetric information was low.

Another possibility is that only selected groups of patients at risk of vascular disease benefit from vitamin D supplementation. The effect of vitamin D on blood pressure in a previous meta-analysis was seen only in those studies in which blood pressure was elevated at baseline11 and patients with type 2 diabetes mellitus seemed to benefit more in terms of blood pressure reduction. Participants in the current study were all hypertensive at baseline, but few had diabetes mellitus. Participants were taking a wide range of antihypertensive agents, thus many of the available biological pathways for blood pressure reduction may have already been engaged. Vitamin D has been posited to exert antihypertensive effects via effects on the renin–angiotensin–aldosterone system, either by direct inhibition of renin24 or by angiotensin-converting enzyme inhibitor-like effects.25 A high percentage of participants were taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists; this may have served to obviate any further benefit of adding vitamin D. Another possibility is that those with different ethnic or genetic backgrounds may respond differently; a recent trial in black Americans showed a reduction in blood pressure with vitamin D3; higher doses of vitamin D produced larger falls in blood pressure.26 The lack of effect seen in this study does not exclude an effect in nonresistant or drug-naive hypertensive patients; such patients may still respond to manipulation of biological pathways by vitamin D that do not respond or have already been used, in treated, resistant patients with hypertension.

Strengths of our study include the randomized, blinded design, the use of 24-hour blood pressure measurements, and the assessment of LV mass index—a key independent marker of vascular events and vascular death. Limitations include the relatively small study size, white study population, lack of follow-up beyond 6 months, and the obscuring effect of multiple treatments; an inevitable limitation when studying patients with resistant hypertension.

### Perspectives

High-dose intermittent oral vitamin D3 therapy did not reduce blood pressure or LV mass in patients with resistant hypertension on multiple antihypertensive agents. Further research could focus on whether larger doses of vitamin D given for longer might be more effective, or whether prespecified subgroups (eg, those with diabetes mellitus or not taking renin–angiotensin system blockers) might still show reductions in blood pressure with vitamin D.

### Acknowledgments

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### Disclosures

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### References


**Novelty and Significance**

**What Is New?**

- Trials of vitamin D supplementation to date have not focused on patients with resistant hypertension; this placebo-controlled trial is the first to do so. There was no reduction in blood pressure or left ventricular hypertrophy after 6 months of high-dose, intermittent oral vitamin D3 supplementation.

**What Is Relevant?**

- Although observational data suggest a link between low vitamin D levels and higher blood pressure, trial results to date have been inconsistent.

These results do not support the use of vitamin D because a therapy for this is difficult to treat group of patients.

**Summary**

This dose and duration of vitamin D were not effective at reducing blood pressure or left ventricular mass in this population of patients with resistant hypertension.
Vitamin D Therapy to Reduce Blood Pressure and Left Ventricular Hypertrophy in Resistant Hypertension: Randomized, Controlled Trial
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ON LINE SUPPLEMENT

VITAMIN D THERAPY TO REDUCE BLOOD PRESSURE AND LEFT VENTRICULAR HYPERTROPHY IN RESISTANT HYPERTENSION – A RANDOMISED CONTROLLED TRIAL

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<table>
<thead>
<tr>
<th>Event category</th>
<th>Vitamin D</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Musculoskeletal</td>
<td>9</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Gastrointestinal</td>
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<td>Respiratory</td>
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<tr>
<td>Skin</td>
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<td>Hypercalcemia*</td>
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<tr>
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*Albumin-adjusted calcium >2.60 mmol/L