treatment might not significantly reduce PPMN after elective PCI in patients with stable angina. However, adjunctive clopidogrel pretreatment could reduce PPMN in patients without chronic stent therapy before elective PCI.

### P681 | BEDSIDE

**Statin therapy is a major determinant of PCSK9 plasma concentration: data from four clinical trials with AMG 145**

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**Purpose:** Proprotein convertase subtilisin kexin type 9 (PCSK9) plays a critical role in the metabolism of low density lipoproteins (LDL), impairing LDL clearance by promoting LDL receptor degradation. Data suggest statins may modulate PCSK9 levels. We tested whether PCSK9 levels were associated with the intensity of statin therapy.

**Method:** We analyzed baseline PCSK9 plasma concentrations in 1335 patients, aged 18-80, in four Phase 2 clinical trials (MENDEL, LAPLACE, RUTHERFORD, GAUSS) with AMG 145, a fully human monoclonal antibody to PCSK9, and examined associations with baseline characteristics, including statin therapy (none, non-intensive, or intensive [defined as simvastatin 80 mg QD, atorvastatin 40 mg QD, rosuvastatin ≥20 mg QD, or any statin plus ezetimibe]).

**Results:** Baseline PCSK9 concentration varied greatly (median 406 ng/mL, IQR 326-493 ng/mL, range 116-1200 ng/mL), but levels were not associated with age, sex, or LDL-C. PCSK9 levels did significantly differ based on statin therapy; medians were 343 ng/mL (IQR 296-408) in patients on no statin, 421 ng/mL (IQR 346-485) for those on non-intensive statin treatments, and 531 ng/mL (IQR 433-645) for those on intensive statin treatments (p-value < 0.0001). In the analyses of log-transformed baseline PCSK9 levels, baseline statin treatment accounted for more than one-quarter (R² = 0.28, p-value < 0.0001) of the variability, more than any other baseline factor.

**Conclusions:** PCSK9 plasma concentrations are higher in patients on statin therapy and highest in those on the most intensive statin or statin plus ezetimibe treatments.

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### P682 | BEDSIDE

**Intolerance to statins and response to PCSK9 inhibition with AMG 145**

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**Purpose:** AMG 145, a fully human monoclonal antibody to PCSK9, significantly reduced LDL-C levels in statin-intolerant patients in the GAUSS trial (NCT01375764). We report the relationship between pre-trial history of intolerance to statins and on-treatment therapeutic response, tolerability, and safety with AMG 145.

**Methods:** This post-hoc intention-to-treat analysis included 157 patients aged 34-75 years who received 4 weekly subcutaneous administrations of AMG 145 or placebo. Participants who had all failed standard statin therapy due to muscle-related side effects, were grouped according to their history of intolerance of one, two, or three or more statins prior to the study.

**Results:** See Table 1.

**Conclusion:** Attempts at statin treatment increased with CVD risk but were not related to tolerability of AMG 145. LDL-C reductions appeared to diminish with the number of failed statins but were still comparable with reductions reported with the highest doses of the most effective statins.

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### P683 | BEDSIDE

**Safety of AMG 145, a fully human monoclonal antibody to PCSK9:**

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**Purpose:** In 4 phase 2 RCTs, AMG 145, a fully human monoclonal antibody to PCSK9 given subcutaneously (SC) every 2 or 4 weeks, robustly reduced LDL-C. We report the prespecified safety analysis across all 4 trials in 1314 patients.

**Methods:** Of 1359 patients randomized, 981 received AMG 145 and 333 placebo for 12 wks; an additional 45 received ezetimibe without placebo injections and hence were excluded. Three trials permitted statins. Serious adverse events (SAEs) and other safety data were collected through 30 days and > 14 days post last dose, respectively.

**Results:** The mean age was 56±12, 56% were women, 60% were on statin. Mean changes in LDL-C ranged from a 40% to 59% across AMG 145 doses. AEs were more frequent with AMG 145 vs. placebo (57% vs 49%) (Table). SAEs rates were similar with no treatment-related SAEs in either group. No relation of AEs to dose/frequency was observed (data not shown). Muscle-related AEs occurred in 6.0% vs 3.9% and CK elevations in 1.4% vs 0.9% of patients receiving AMG 145 vs placebo. No neutralizing antibodies were detected. Injection-site reactions and IT elevations were similar between groups.

**Conclusions:** In a large pooled analysis of 4 phase 2 trials, the overall safety

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### Table 1

<table>
<thead>
<tr>
<th>Intolerance to statins (number of statins)</th>
<th>EZE/placebo</th>
<th>EZE/AMG 145</th>
<th>AMG 145 effects in statin-intolerant patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>(n=7)</td>
<td>(n=14)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>Statin at baseline, n (%)</td>
<td>12 (17)</td>
<td>7 (10)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Decrease in LDL-C from baseline at week 12, mean % (95% CI)</td>
<td>21 (9-33)</td>
<td>62 (53-70)</td>
<td>51 (47-56)</td>
</tr>
<tr>
<td>Decrease in apolipoprotein B from baseline at week 12, mean % (95% CI)</td>
<td>17 (8-36)</td>
<td>50 (42-58)</td>
<td>43 (38-48)</td>
</tr>
<tr>
<td>Treatment emergent adverse events (AEs), n (%)</td>
<td>4 (57)</td>
<td>10 (50)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Treatment-related AEs, n (%)</td>
<td>1 (14)</td>
<td>2 (10)</td>
<td>2 (13)</td>
</tr>
</tbody>
</table>

**EZE/placebo:** oral ezetimibe 10 mg once daily + subcutaneous placebo QW; **EZE/AMG 145:** oral ezetimibe 10 mg once daily + SC AMG 145 420 mg Q4W; **AMG 145:** SC AMG 145 280 mg, 350 mg, or 420 mg Q4W; **NCEP:** National Cholesterol Education Project; **LDL-C:** low-density lipoprotein cholesterol; **CI:** confidence interval.