

## Intensive versus Standard Blood Pressure Goals for Treating Hypertension: A Review of Recent Landmark Trials

Jimmy Ortiz, PharmD

**H**ypertension affects 80 million adults in the U.S. and >1 billion adults worldwide, and is a huge contributor to morbidity and mortality.<sup>1</sup> In the U.S. alone, hypertension causes or contributes to roughly 1,212 deaths every day.<sup>2</sup> Among individuals with hypertension, 83% are aware of their condition and 77% take medications for treatment.<sup>3</sup> However, only 54% of people diagnosed with hypertension have their blood pressure (BP) controlled to goal levels.

Current hypertension treatment guidelines in the U.S. and elsewhere generally provide sweeping recommendations for BP goals across large groups of individuals with hypertension. For example, the Joint National Committee (JNC) 8 guidelines, published in 2014, recommends a BP goal <150/90 mm Hg for all patients aged ≥60 years without diabetes or chronic kidney disease (CKD).<sup>3</sup> However, other guidelines both within and outside the U.S. recommend BP goals <140/90 mm Hg for the general hypertensive population up to an age of 80 years.<sup>3,4</sup> Blood pressure goals also differ across guidelines for patients with diabetes or CKD, where goals are generally lower than for the general hypertensive population.<sup>5,6</sup> Thus, controversy currently exists regarding the optimal BP goals for the treatment of hypertension.

In the previous 5 years, two landmark randomized controlled trials (RCTs), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Systolic blood Pressure Intervention Trial (SPRINT), have shed further light on BP goals in hypertensive patients with and without diabetes, respectively. The purpose of the article is to highlight the existing evidence informing JNC 8 BP goal recommendations and to review the ACCORD and SPRINT trials, including a discussion of how these trials may change subsequent hypertension guideline recommendations.

### BP GOALS IN NON-DIABETIC PATIENTS

#### Previous Studies

Six randomized controlled trials (RCTs) were used by the JNC 8 panel to recommend a SBP goal for non-diabetic patients with hypertension.<sup>7-12</sup> The recommendation to treat to a SBP goal <150 mm Hg for individuals in the general population ≥60 years old was based on the Hypertension in the Very Elderly Trial (HYVET), Systolic Hypertension in Europe trial (Syst-Eur), Systolic Hypertension in the Elderly Program (SHEP), Japanese Trial to Assess Optimal Systolic Blood Pressure in the Elderly Hypertensive Patients (JATOS), Valsartan in the Elderly Isolated Systolic Hypertension study (VALISH), and Control of Systolic Blood Pressure in non-diabetic patients with hypertension (CARDIO-SIS).

The HYVET trial was conducted with participants who were ≥80 years and older with a SBP ≥160 mm Hg.<sup>8</sup> The target BP of this study was 150/80 mm Hg, with the primary endpoint being fatal or nonfatal stroke. The results showed that the active treatment group was associated with a 30% reduction in the primary endpoint, 21% decrease in all-cause mortality, and 23% decrease in death from CV causes. Both Syst-Eur and SHEP trials studied >60 years old with isolated systolic hypertension. Syst-Eur and SHEP had a reduction in incidence of stroke of 42% and 36%, respectively.<sup>7,9</sup> The HYVET and SHEP trials provide evidence which supports a SBP goal <150 mm Hg, although the average SBP in the treatment groups were 143 to 144 mm Hg.

The JATOS trial was composed of patients who were assigned to one of two groups: a strict regimen (SBP goal <140 mm Hg) or mild regimen (SBP ≥140 mm Hg).<sup>10</sup> The investigators concluded that there was no significant difference in the primary endpoints, which were stroke, CV disease and renal failure between the groups. Similarly, the VALISH trial compared strict BP control (<140 mm Hg) to moderate BP control (≥140 to <150 mm Hg) in decreasing CV morbidity and mortality, and concluded that there was no significant difference in rate of the primary outcome between the two groups.<sup>11</sup> Unlike the above-mentioned trials, the CARDIO-SIS trial compared patients without diabetes who were assigned to a standard target (SBP <140 mm Hg) or strict target (SBP <130 mm Hg). The primary endpoint of this study was incidence of left ventricular hypertrophy. This trial suggested that the likelihood of left ventricular hypertrophy is significantly reduced with tighter BP goal. However, the JATOS and VALISH studies suggested that a SBP goal of <140 mm Hg did not provide additional benefits.

Importantly, the SBP goal of <140 mm Hg for individuals <60 years old is based on expert opinion since the panel did not find sufficient evidence to support a specific SBP goal.<sup>5</sup> Specifically, at the time of the JNC 8 systematic review, no RCTs had compared a SBP goal of <140 mm Hg to a higher or lower goal in patients aged <60 years. The panel reasoned that having a similar



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**Table 1 | Serious adverse events in the SPRINT trial.<sup>19</sup>**

Variable	Intensive SBP Goal (N=4678)	Standard SBP Goal (N=4683)	Hazard Ratio (Intensive vs. Standard)	p value
Serious adverse events <sup>a</sup>	1793 (38.3)	1736 (37.1)	1.04	0.25
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall <sup>b</sup>	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure	193(4.1)	117 (2.5)	1.66	<0.001

SBP = systolic blood pressure.

<sup>a</sup>A fatal or life-threatening event, which resulted in significant or persistent disability, which required or prolonged a hospitalization.

<sup>b</sup>Fall requiring evaluation in an emergency department or hospitalization.

goal to patients with CKD or diabetes may assist clinicians in guideline implementation.<sup>5</sup>

### SPRINT

The recently published SPRINT trial was a RCT investigating the effects of an intensive SBP goal (<120 mm Hg) versus standard SBP goal (<140 mm Hg) in patients with hypertension who were at high risk for cardiovascular (CV) events.<sup>19</sup> The study enrolled 9,361 patients who were aged  $\geq 50$  years with a baseline SBP between 130 and 180 mm Hg (specific threshold dependent on number of antihypertensive agents being used), and at increased risk of a CV event. Individuals with at least one of the following were considered to be at increased CV risk: CKD (not including polycystic kidney disease), estimated glomerular filtration rate (eGFR) between 20 and 59 mL/min/1.73 m<sup>2</sup>, subclinical or clinical CV disease (excluding stroke), a 10-year risk of CV disease  $\geq 15\%$  using the Framingham risk calculator, or age  $\geq 75$  years.<sup>19</sup> Individuals with a diagnosis of diabetes, a history of stroke, symptomatic HF within the past 6 months, a medical condition with an estimated survival <3 years, a previous transplant, or an active pregnancy were excluded from the study. The primary outcome was first occurrence of a myocardial infarction (MI), other acute coronary syndromes, stroke, HF, or death from CV causes. The secondary outcomes included death from any cause, renal function decline, development of end stage renal disease (ESRD), dementia or decrease in cognitive function, and small vessel cerebral ischemic disease. Kidney function was assessed at baseline and renal outcome analyses were stratified according to the presence or absence of CKD at the beginning of the trial. The renal outcome for participants with CKD at baseline (defined as baseline eGFR <60 mL/minute/1.73 m<sup>2</sup>) was a composite of a decrease in the eGFR by  $\geq 50\%$  or the development of ESRD requiring dialysis or a kidney transplant. In participants without CKD (defined as having eGFR  $\geq 60$  mL/minute/1.73 m<sup>2</sup>), the renal outcome was defined as an eGFR decrease by  $\geq 30\%$  to <60 mL/minute/1.73 m<sup>2</sup>. The incidence of albuminuria was also a pre-specified renal outcome. Investigators were provided with treatment algorithms and suggestions on pharmacotherapy, but the choice of agent and titration schedule was at the discretion of the site investigator.

Baseline characteristics between both groups were generally similar, including similar baseline SBP (mean  $\pm$  SD, 139.7  $\pm$  15.8

in the intensive SBP vs. 139.7  $\pm$  15.4 in the standard SBP arms) and DBP (78.2  $\pm$  11.9 in the intensive SBP arm vs. 78.0  $\pm$  12.0 in the standard SBP arm). However, statin use differed between groups, with 42.6% in the intensive SBP arm versus 44.7% in the standard SBP arm ( $p=0.04$ ). After 1 year, the mean SBP in the intensive SBP goal group was 121.4 mm Hg compared to 136.2 mm Hg in the standard SBP goal group; the mean difference between treatment groups was 14.8 mm Hg.<sup>19</sup> The mean DBP at 1 year was 68.7 mm Hg in the intensive SBP goal group compared to 76.3 mm Hg in the standard SBP goal group, for a mean between-group difference of 7.6 mm Hg. The trial was stopped early after an interim review, which showed that treatment to an intensive SBP goal had lower rates of the primary composite outcome compared with treatment to a standard SBP goal. After a mean follow-up of 3.26 years, the mean SBP was 121.5 mm Hg in the intensive treatment versus 134.6 mm Hg in the standard group with a mean number of BP medications of 2.8 and 1.8, respectively. The primary outcome occurred in 562 participants overall, including in 243 patients in the intensive SBP goal group and 319 in the standard SBP goal group (adjusted hazard ratio [HR], 0.75; 95% CI, 0.64 to 0.89;  $p<0.001$ ). A total of 365 deaths (all-cause) occurred throughout the trial: 155 in the intensive SBP goal group and 210 in the standard SBP goal group (adjusted HR, 0.73; 95% CI, 0.60 to 0.90;  $p=0.003$ ). The authors reported a 43% reduction in the relative risk of death from cardiovascular causes for patients in the intensive SBP goal group compared to the standard SBP goal group ( $p=0.005$ ).<sup>18</sup> The numbers needed to treat (to the lower SBP goal) to prevent a primary outcome event, death from any cause, and death from CV causes over 3.26 years, were 61, 90, and 172, respectively. Comparing treatment arms among participants with CKD at baseline, no significant between-group difference was observed in the composite outcome of  $\geq 50\%$  decrease in eGFR or development of ESRD. However, among patients without CKD at baseline, patients in the intensive SBP goal group had a higher incidence of the renal outcome (1.21% per year) compared to a 0.35% per year incidence rate among those in the standard SBP goal group (adjusted HR, 3.49; 95% CI, 2.44 to 5.10;  $p<0.001$ ). There was no significant difference in serious adverse events between the treatment groups; however, the intensive SBP goal was associated with more frequent hypotension, syncope, and electrolyte abnormalities (Table 1).<sup>19</sup>

The SPRINT trial showed that older, non-diabetic adults with hypertension would benefit from a lower SBP goal than the currently recommended SBP goals of <140 or <150 mm Hg (depending on the guideline).<sup>19</sup> Participants assigned to the intensive SBP goal had a 25% lower relative risk of the primary outcome, largely driven by lower rates of HF (38% relative risk reduction), a 27% lower risk of death from any cause, and a 43% lower risk of death from CV causes. The SPRINT trial raised important issues worth considering. First, it is worth noting that in the United States, target BP goals of <140/90 mmHg is accomplished in around 50% of the population.<sup>20</sup> Thus, a lower BP target would be more challenging to achieve. Second, in SPRINT, the median SBP was slightly above 120 mm Hg in the intensive-treatment group, which implies that more than half of the participants had a SBP >120 mmHg. Therefore, achieving a target SBP <120 mm Hg would be more difficult to achieve in the general population than the standard SBP <140 mm Hg. The biggest strength of this trial was the large sample size which included patients aged >75 years (28% of the SPRINT population). However, this study lacks generalizability to those with a history of diabetes, previous stroke, or age <50 years.<sup>19</sup> Additionally, questions have been raised about whether the method used to measure BP in SPRINT is sufficiently similar to typical clinic BP measurement to warrant targeting clinic SBP <120 mm Hg.

## BP GOALS IN DIABETICS

### Prior Studies

Four trials informed the JNC 8 recommendations of SBP <140 mm Hg and DBP <90 mm Hg in individuals aged ≥18 years with diabetes<sup>5</sup>: SHEP, Syst-Eur, UK Prospective Diabetes Study Group (UKPDS) and ACCORD-BP.<sup>7,9,21,22</sup> The panel considered these trials to be of moderate-quality and found that no RCTs addressed whether treating to a SBP goal of <140 mm Hg or a higher goal such as <150 mm Hg improves health outcomes in this population. Thus, in the absence of such evidence, the panel recommended the goals listed above based on expert opinion.

SHEP enrolled patient aged ≥60 years with a SBP between 160 and 219 mm Hg and DBP <90 mm Hg.<sup>9</sup> The treatment goal was to decrease SBP by ≥20 mm Hg from baseline and to below 160 mm Hg with the use of a diuretic-based (chlorthalidone) regimen. The primary endpoint was incidence of nonfatal and fatal stroke and the secondary endpoints were CV and coronary morbidity and mortality, all-cause mortality and quality of life. The baseline mean BP was 170/77 mm Hg and 10% of the participants had diabetes. The decrease in BP from baseline averaged 26/9 mm Hg for the active treatment group and 15/4 mm Hg for the placebo group. After an average of 5 years, the mean SBP was 155 mm Hg in the placebo group and 143 mm Hg in the active treatment group. The 5-year mean DBP was 72 mm Hg in the placebo group and 68 mm Hg in the treatment group. Investigators found that antihypertensive medications reduced the incidence of stroke by 36%, fatal or nonfatal MI and coronary heart disease by 27%, all CV disease by 32%, and all-cause mortality by 13%.<sup>9</sup>

Syst-Eur investigated BP lowering treatment for patients ≥60 years old with isolated systolic hypertension (SBP ≥160 mm Hg and DBP <95 mm Hg).<sup>7</sup> Interventions used in this trial were nitrendipine, with the possible addition of enalapril and hydrochlorothiazide versus placebo. In this trial, around ten percent of the subjects had diabetes. The primary endpoints were fatal and

nonfatal stroke and the secondary endpoints were death, stroke, retinal hemorrhage or exudates, MI, CHF, aortic aneurism and renal insufficiency. At the 2-year follow up visit, sitting SBP/DBP decreased by 13/2 mm Hg in the placebo group and 23/7 mm Hg in the treatment group. The mean sitting BP achieved was 161/84 mm Hg in the placebo group and 151/79 mm Hg in the treatment group. There was a between-group difference of 10 mm Hg in SBP and 5 mm Hg in DBP. Active treatment decreased all strokes by 42% and cardiac endpoints such as death and non-fatal events by 26%.<sup>7</sup>

UKPDS compared tight BP control (BP goal <150/85 mm Hg) with more lenient BP control (<180/105 mm Hg) in patients with hypertension and type 2 diabetes mellitus.<sup>21</sup> Participants in the tight BP control group achieved a mean BP of 144/82 mm Hg, compared with the more lenient BP control group (mean BP, 154/87 mm Hg;  $p < 0.0001$ ), and corresponding lower rates of major diabetes endpoints, stroke, and death due to diabetes, suggesting that more aggressive BP lowering, at least to <150/85 mm Hg, is preferred in patients with hypertension and type 2 diabetes.<sup>21</sup>

The Hypertension Optimal Treatment (HOT) trial was considered by the JNC 8 panel, but was deemed low quality since the data of the diabetic population within the HOT trial was a post hoc analysis. The HOT trial randomly assigned 18,790 patients with hypertension (with or without diabetes) to one of three diastolic BP (DBP) goals: <90 mm Hg vs. <85 mm Hg vs. <80 mm Hg.<sup>23</sup> Among the subset of patients with diabetes (8.4% of overall HOT population), the researchers found that the group assigned to the lowest DBP goal (<80 mm Hg) had the lowest risk of the composite CVD morbidity and mortality outcome. However, actual achieved BP difference between DBP goal groups was quite small, averaging only 1-2 mm Hg between the highest and lowest BP goal arms, and the evidence was deemed low quality due to the *post hoc* nature of the analysis for a small group.

### ACCORD BP

The ACCORD study was a RCT conducted at 77 clinical sites in the U.S. and Canada.<sup>22</sup> A total of 10,241 participants with type 2 diabetes and at high CV risk were enrolled in the trial. All of the individuals were randomly assigned to intensive or standard glycemic groups (known as the ACCORD glycemia trial). Furthermore, 5,518 of the participants received (in a 2-by-2 factorial design) either simvastatin plus fenofibrate or simvastatin plus placebo (ACCORD lipid trial) and 4,733 participants were randomly assigned to either an intensive SBP goal (<120 mm Hg) or standard SBP goal (<140 mm Hg) in the ACCORD BP trial. Participants were included in the trial if they had a diagnosis of type 2 diabetes with an A1C ≥7.5%, and were either ≥40 years old with CV disease, or ≥55 years old with atherosclerosis, left ventricular hypertrophy, albuminuria, or ≥2 risk factors for CV disease (hypertension, obesity, smoking, or dyslipidemia). Additional eligibility for the ACCORD BP trial included a SBP between 130 and 180 mm Hg, use of ≤3 antihypertensive medications, and a 24-hour protein excretion rate <1 gram. Exclusion criteria included a body mass index (BMI) >45 kg/m<sup>2</sup>, serum creatinine (SCr) >1.5 mg/dL, or other serious illnesses.<sup>22</sup> The primary outcome was the first occurrence of a major CV event (MI, nonfatal stroke, or CV-related death).<sup>22</sup> Secondary outcomes were (separately) nonfatal MI, stroke, death from any cause, death from a CV cause, and several composite outcomes. Investigators were encouraged to use any antihypertensive agent with proven CV benefit in patients with diabetes to achieve BP goals.

**Table 2 | Serious adverse events in the ACCORD BP trial.<sup>22</sup>**

Events	Intensive SBP Goal (N=2362)	Standard SBP Goal (N=2371)	p value
Event attributed to blood-pressure medications	77 (3.3%)	30 (1.27%)	<0.001
Hypotension	17 (0.07%)	1 (0.04%)	<0.001
Syncope	12 (0.05%)	5 (0.21%)	0.10
Bradycardia or arrhythmia	12 (0.05%)	3 (0.13%)	0.02
Hyperkalemia	9 (0.4%)	1 (0.04%)	0.01
Angioedema	6 (0.3%)	4 (0.17%)	0.55
Renal failure	5 (0.2%)	1 (0.04%)	0.12
End stage renal disease or need for dialysis	59 (2.5%)	58 (2.4%)	0.93

Data are presented as number (%).

Baseline characteristics between both groups were generally similar, including similar baseline SBP (mean  $\pm$  SD, 138.9  $\pm$  16.3 in the intensive SBP vs. 139.4  $\pm$  15.8 in the standard SBP arms;  $p=0.34$ ) and DBP (75.7  $\pm$  10.7 in the intensive SBP arm vs. 75.8  $\pm$  10.3 in the standard SBP arm;  $p=0.87$ ). However, total cholesterol and low-density lipoprotein (LDL) was modestly higher in the intensive SBP arm.<sup>22</sup> After 16 months, the average SBP was 119.3 (95% CI, 118.9 to 119.7) mm Hg in the intensive SBP group and 133.5 (95% CI, 133.1 to 133.8) mm Hg in the standard SBP group; resulting in a net difference of 14.2 (95% CI, 13.7 to 14.7) mm Hg. The mean DBP was 64.4 (95% CI, 64.1 to 64.7) mm Hg in the intensive SBP group and 70.5 (95% CI, 70.2 to 70.8) mm Hg in the standard SBP group, for a mean difference of 6.1 (95% CI, 5.7 to 6.5) mm Hg. The primary outcome occurred at similar rates between the two groups: 1.87% per year in the intensive SBP group and 2.09% per year in the standard SBP group (HR 0.88; 95% CI, 0.73 to 1.06;  $p=0.20$ ). However, the rate of nonfatal stroke was significantly lower in the intensive SBP group compared to the standard SBP group (0.30% per year vs. 0.47% per year, respectively;  $p=0.03$ ). The rate of death from any cause was similar in both groups at 1.28% in the intensive SBP group and 1.19% in the standard SBP group (HR 1.07; 95% CI, 0.85 to 1.35;  $p=0.55$ ).<sup>22</sup>

Several important limitations make interpreting the results of the ACCORD BP trial challenging. First, the event rate detected in the standard therapy arm was 50% lower than what was predicted in the pre-trial power analyses.<sup>22</sup> This lower-than-expected event rate may have been due to the use of statins in the ACCORD lipid trial, as well as the inclusion criteria, which placed participants with dyslipidemia into the ACCORD lipid trial, thus, selecting individuals who were lower risk into the ACCORD BP trial. Additionally, possible harm was associated with the intensive SBP goal, including higher rates of serious adverse events (Table 2), since more medications were used in this arm (mean, 3.4 antihypertensive medications/person) versus the standard SBP goal arm (mean, 2.1 antihypertensive medications/person).<sup>22</sup>

### REMAINING UNANSWERED QUESTION

An important remaining question is whether the SPRINT trial results apply to populations that were excluded from the trial. For example, should SPRINT findings be applicable to diabetic patients (i.e., if ACCORD was flawed) or is there really a differ-

ence between these hypertension phenotypes with regard to BP goals? The difference in outcomes between these two trials might be due to the ACCORD study design. ACCORD participants had a lower CV risk profile and were younger. The patients in the ACCORD BP arm with dyslipidemia were excluded from the BP trial, which additionally made them lower risk. Lastly, patients that had a serum creatinine  $>1.5$  mg/dL were excluded from the ACCORD trial due to the use of metformin as part of the treatment of diabetes. The ACCORD trial was solely diabetic patients and the SPRINT trial excluded these individuals. Additionally, the ACCORD trial had a smaller sample size of participants than SPRINT (4733 versus 9361, respectively). In contrast to the results of the SPRINT trial, there was no statistically significant, CV or mortality benefit (except for stroke), in individuals treated to an intensive BP goal in the ACCORD trial. The possibility of an inherent difference in CV benefits of a lower SBP target between diabetics and those without diabetes, is possible, but seems unlikely.

Interestingly, results on the long-term follow-up from ACCORD BP, the ACCORD Follow-On study (ACCORDION), were presented at the American Heart Association scientific session in 2015.<sup>24</sup> The ACCORDION study evaluated the long-term effect of intensive versus standard BP lowering on the incidence of CV events or death. After the ACCORD trial was completed, 3,957 of its participants were followed beyond the original trial duration. The results showed that individuals who were in the intensive BP arm experienced a benefit if they were also not in the intensive glycemia arm. Conversely, those in the intensive SBP goal did not have any benefits if they were included in the intensive glycemia arm. These new results suggest that there is a benefit in targeting an intensive SBP goal of  $<120$  mm Hg for patients at high CV risk with diabetes.

### CONCLUSION

The target SBP for patients with or without diabetes has been uncertain due to lack of data. The National Heart, Lung, and Blood Institute expert panel developed the hypothesis that a lower SBP goal ( $<120$  mm Hg) would reduce more hypertension-related clinical events than the current standard SBP goal ( $<140$  mm Hg) among patients without diabetes. While SPRINT showed a clear benefit, a more aggressive approach to BP lowering may result in more adverse effects. Therefore, individualizing treat-

ment based on patient composition, tolerability of medications, and medical conditions while also weighing the risks and benefits of a lower BP goal must be considered by providers.

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## EDITOR'S CORNER

### FDA Updates Label to Limit Fluoroquinolone Use in Light of Risks

The US Food and Drug Administration (FDA) is updating labels for fluoroquinolones given the risk for disabling and potentially permanent adverse events. This update includes a boxed warning outlining the serious side effects associated with fluoroquinolone use. These label changes are underscoring that the risks generally outweigh the benefits for patients with uncomplicated infections, such as sinusitis, bronchitis, and uncomplicated urinary infections.

Fluoroquinolone use has been associated with serious side effects, including tendonitis, tendon rupture, peripheral neuropathy, QT prolongation, torsades de pointes, and hypersensitivity. These adverse effects can occur simultaneously, and this update by the FDA aims to limit the use of fluoroquinolone in uncomplicated infections that can be treated by other options.

Continual investigation will be done by the FDA in light of these potentially devastating adverse effects. Patients should be informed to contact their physicians immediately if they experience any of the above side effects during treatment. Alternative antibiotics should be used in favor of fluoroquinolone in patients with uncomplicated infections, and the use of fluoroquinolones should be reserved when other antibiotics have been exhausted.

#### For additional information:

- FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effect that can occur together. US Food and Drug Administration Web site. <http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm>. Published May 12, 2016. Updated June 7, 2016. Accessed July 15, 2016.
- FDA announces safety labeling changes for fluoroquinolones. US Food and Drug Administration. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm500325.htm>. Published May 12, 2016. Updated May 12, 2016. Accessed July 15, 2016.

## PERSONALIZED MEDICINE CORNER

## Sickle cell disease: Personalizing pain management

Use of codeine in pediatrics has largely declined because of its potential for severe or fatal respiratory depression in patients with the ultra-rapid metabolizer *CYP2D6* genotype.<sup>1</sup> In these patients, codeine is converted rapidly to its more potent form, morphine. Postoperative deaths have been reported in such patients and led to an FDA black box warning on its use in children.<sup>2-4</sup> However, codeine is still preferred as a milder potency, non-schedule II opioid in select pediatric groups such as those with sickle cell disease.<sup>5</sup> In these populations, *CYP2D6* pharmacogenetic data can be used to identify patients with a 'high-risk' *CYP2D6* genotype that places them at increased risk for adverse effects (i.e., *CYP2D6* ultra-rapid metabolizers) or poor therapeutic response to codeine (i.e., *CYP2D6* poor metabolizers).<sup>1</sup>

A recent report in *Pediatrics* describes the use of genotype-guided analgesic selection for codeine in pediatric patients with sickle cell disease in a research hospital.<sup>6</sup> In this clinical service, *CYP2D6* genotype results and assigned phenotypes were made available to prescribers through the electronic health record (EHR). Clinical guidance was based on Clinical Pharmacogenetics Implementation Consortium guidelines,<sup>1</sup> and drug therapy recommendations for high-risk *CYP2D6* genotypes were communicated to prescribers via clinical decision support alert and a pharmacist consultation note.

A total of 75% (621 of 830) of patients with sickle cell disease were genotyped. Of these individuals, 1.4% and 7% were categorized as poor metabolizers and ultra-rapid/possible ultra-rapid metabolizers, respectively. While codeine was used in 32% of patients without a high-risk *CYP2D6* genotype, it use was rare in those with a high-risk genotype indicating good physician acceptance of pharmacogenetic test results and related recommendations. Six of the 53 patients with a high-risk *CYP2D6* genotype were initially prescribed codeine, which triggered a clinical decision support alert for the prescriber. This alert prompted a therapy change in 5 of these patients, with only 1 high-risk *CYP2D6* genotype patient receiving codeine (patient was noted to have tolerated codeine in the past). The most common alternative used for codeine was hydrocodone/acetaminophen.

The practice model used in this study is similar to strategies employed at UF Health to order and support pharmacogenetic testing for *CYP2D6*, *CYP2C19* and other genes. Contact the UF Health Personalized Medicine Program ([PMP-HELP@ctsi.ufl.edu](mailto:PMP-HELP@ctsi.ufl.edu)) for more information about these tests or for assistance interpreting pharmacogenetic test results clinically.

## References:

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*Co-Editors:* Larisa Cavallari, PharmD; Kristin Weitzel, PharmD;  
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