



TICAGRELOR: THE FIRST ORAL, REVERSIBLE P2Y₁₂ RECEPTOR ANTAGONIST FOR ACS

Harrison Saull, Pharm.D. Candidate

Acute coronary syndromes (ACS) are life-threatening cardiovascular disorders with symptoms consistent with acute myocardial ischemia.¹ ACS, which includes unstable angina pectoris (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), affects nearly 1.5 million individuals in the United States annually.^{1,2} In 2011, an estimated 785,000 people in the United States will have a first heart attack and 470,000 will have a recurrent attack.² The underlying cause of most cases of ACS is atherosclerosis, a process driven by endothelial dysfunction that involves the accumulation of plaque within the arteries and subsequent luminal narrowing.³ ACS results from plaque rupture and the formation of a platelet-rich thrombus that limits coronary blood flow.^{1,3}

The role of platelets in the development of atherothrombosis and ACS is pivotal.⁴ For many years, aspirin has been a cornerstone therapy for ACS treatment due to its ability to prevent adverse ischemic events.¹⁻⁴ For the past two decades, clinical practice guidelines have advocated for dual antiplatelet therapy in ACS patients with aspirin and a P2Y₁₂ receptor inhibitor.^{1-3,5,6} Adenosine diphosphate (ADP) is a key mediator of thrombosis and has a crucial role in platelet aggregation, which it mediates predominantly via stimulation of the platelet P2Y₁₂ receptor.⁵ In addition to standard antithrombotic treatment, patients with ACS may re-

ceive percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG) surgery.^{1,3}

Dual antiplatelet therapy with clopidogrel (Plavix®) and aspirin has become the standard of care for patients with ACS.^{5,6} However, clopidogrel has several important limitations. Clopidogrel is a pro-drug that requires hepatic conversion, leading to delay in onset of action.⁷ Also, interindividual variability with regard to response, drug interactions, and suboptimal potency has been demonstrated with clopidogrel therapy.⁸ Ultimately, patients who have lower degrees of platelet inhibition with clopidogrel may be at increased risk of adverse ischemic outcomes.

Despite increased knowledge in cardiovascular pathophysiology and advances in pharmacotherapy options, ACS is still associated with significant mortality and morbidity. The role of P2Y₁₂ receptor inhibitors in ACS continues to evolve with the approval of ticagrelor. Ticagrelor is a new oral antiplatelet agent FDA indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS.⁹ Ticagrelor was approved for marketing in the U.S. in July 2011 under the trade name Brilinta® and is manufactured by AstraZeneca Pharmaceuticals.⁹

Ticagrelor's recent approval provides clinicians with a new agent to reduce the risk of secondary cardiovascular events. This article will review ticagre-

INSIDE THIS ISSUE:

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lor's pharmacology and pharmacokinetics, outline ticagrelor's efficacy and safety data, and summarize dosing and cost.

PHARMACOLOGY

Ticagrelor is a cyclo-pentyltriazolo-pyrimidine, a new chemical drug class of antiplatelet agents that differs from thienopyridines (i.e. clopidogrel).⁹ Ticagrelor is the first reversible oral P2Y₁₂ receptor antagonist that blocks ADP-induced platelet aggregation.¹⁰ In contrast to thienopyridines, which irreversibly bind to the P2Y₁₂ receptor for the lifetime of the platelet, ticagrelor binds reversibly and rapidly.^{7,10}

PHARMACOKINETICS

The pharmacokinetics of ticagrelor has been extensively studied in healthy volunteers, those with ACS, and in patients with renal or hepatic insufficiency.^{10,11,12,17} Ticagrelor is rapidly absorbed after oral administration and differs from currently available P2Y₁₂ antagonists in that it does not require hepatic biotransformation. Ticagrelor is metabolized to an equipotent, active metabolite (AR-C124910XX) by CYP3A4 enzymes.¹⁰ Ticagrelor is further metabolized to an inactive metabolite and glucuronide derivative that are eliminated in the urine. Ticagrelor and AR-

C124910XX are eliminated in the feces, with less than 1% found in the urine, suggesting that renal dose adjustment is not necessary.¹¹ Individuals with mild hepatic insufficiency have shown moderate increases in the levels of ticagrelor and the metabolite compared with controls. Nevertheless, this increase creates no subsequent effects on the pharmacodynamics of the drug or clinical outcomes.¹² Patients with moderate or severe hepatic impairment have not been evaluated, and consequently use of ticagrelor is contraindicated in these patients.⁹

Plasma concentrations of ticagrelor and its active metabolite exhibit linear, dose-proportional pharmacokinetics that are stable and predictable at steady state.¹¹ Nearly complete inhibition of platelet aggregation (IPA), 85%- 95%, is observed at 2 to 4 hours following oral administration of ticagrelor (**Table 1**).^{10,11} Ticagrelor has a half-life of 7 to 8.5 hours, with the metabolite lasting up to 12 hours.^{11,12} Pharmacokinetic parameters have not been shown to be significantly altered by sex, age, or administration with high-fat meals.¹¹

CYP 3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. In vivo metabolism studies reveal that ticagrelor is a weak inhibitor of CYP3A4, potential activator of CYP3A4, and inhibitor of the p-glycoprotein (P-gp) transporters.¹³ Concomitant administration of ticagrelor and CYP3A4 inhibitors and inducers should be avoided (**Table 2**).¹³

CLINICAL TRIALS

The clinical safety and efficacy of ticagrelor in patients with ACS has been evaluated in two randomized, double-blinded, multicenter trials, known as DISPERSE-2¹⁴ and PLATO.¹⁵

Phase II Dose- Ranging Study (DISPERSE-2)

Cannon and colleagues assessed the safety and efficacy of ticagrelor in 990 patients with non-ST-elevation ACS receiving aspirin and standard therapy for ACS.¹⁴ Patients were randomized in a double-blinded manner to receive ticagrelor 90 mg twice daily, ticagrelor 180 mg twice daily, or clopidogrel 300 mg initially followed by 75 mg once daily for up to 3 months. In addition, patients in the ticagrelor groups were randomized to receive a 270 mg loading dose of ticagrelor or no loading dose.

The primary outcome of the study was to evaluate total bleeding events within the first four weeks of treatment, differentiating between major and minor bleeding. No significant differences were shown in the primary outcome between the three treatment groups

Table 1 | Pharmacokinetic properties of ticagrelor^{9,11}

Property	Ticagrelor	AR-C124910XX (active metabolite)
Absorption	Rapid	
Bioavailability (%)	36	
C _{max} (ng/mL) ^a	529	
AUC (ng • h/mL) ^a	3451	
t _{max} (h)	1-5	1.5- 5
Protein Binding (%)	>99	
Vd (L)	88	
Metabolism	Hepatic via CYP3A4/5	
Excretion	Feces (58%); urine (26%); actual amount of parent drug and active metabolite excreted in urine was <1% of total dose administered	
t _{1/2} (h)	7-12	8.5-10

AUC= area under the plasma concentration- time curve; C_{max}= maximum plasma concentration; t_{1/2}= elimination half-life; t_{max}= time to maximum concentration; Vd= volume of distribution.

^a Following administration of oral ticagrelor 90 mg in the fasted state.

at weeks 4 and 12. Although the finding was not statistically significant, the ticagrelor 180 mg group had a lower risk of MI at weeks 4 and 12. Overall, the study demonstrated similar safety and tolerability for ticagrelor compared with clopidogrel. This study was relatively small, however, and not powered to detect differences in efficacy end points. The higher rates of dyspnea and electrocardiographic disturbances (asymptomatic ventricular pauses) in the 180 mg group led to the selection of the 90 mg twice daily regimen for further clinical development in the PLATO trial.

Phase III Superiority Trial (PLATO)

PLATO (PLATElet Inhibition and Patient Outcomes) was a phase III multicenter, randomized, double-blind trial of more than 18,000 patients hospitalized for ACS (with or without ST-segment elevation).¹⁵ Patients were randomized within 24 hours of ACS onset to receive either ticagrelor or clopidogrel. All patients received concomitant daily aspirin, with a recommend loading dose of 325 mg and maintenance dose of 75 to 100 mg daily. The daily dose of aspirin permitted for 6 months after stent placement was 325 mg. Ticagrelor was given as a 180 mg loading dose followed by 90 mg twice daily thereafter. Patients in the clopidogrel group received a 300-mg loading dose followed by 75 mg daily thereafter. Patients undergoing PCI after randomization received an additional dose of their study drug at the time of PCI. Patients who underwent PCI more than 24 hours after randomization received an additional 300 mg of clopidogrel or 90 mg of ticagrelor. In patients undergoing CABG, it was recommended that the study drug be withheld for 5 days in the clopidogrel group and for 24 to 72 hours in the

ticagrelor group. The primary efficacy end point was the composite of vascular death, MI, and stroke. The primary safety end point was major bleeding.

The primary end point occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs 11.7% at 12 months; HR, 0.84; 95% CI, 0.77–0.92; $P < 0.001$). This difference was apparent as early as 30 days after the start of treatment, and was driven by statistically significant reductions in both vascular death and MI ($P < 0.01$ for both). All-cause mortality was also less with ticagrelor (4.5% vs 5.9%; $P < 0.001$). The ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major bleeding as defined in the trial (11.6% and 11.2%, respectively; $P = 0.43$). However, there was a higher rate of non-CABG-related major bleeding with ticagrelor compared with clopidogrel according to the study criteria (4.5% vs 3.8%, $P = 0.03$), including more instances of fatal intracranial bleeding.

Based on the results of the PLATO study, treating 1,000 ACS patients with ticagrelor instead of clopidogrel would prevent 11 vascular deaths and 11 MIs at the cost of 6 non-CABG-related major bleeding episodes. The overall results of this study demonstrate that in patients with ACS, treatment with ticagrelor compared to clopidogrel significantly reduced the rate of death from vascular causes and MI, without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.¹⁵

Other Studies

A number of subgroup analyses originated from PLATO. These analyses involved patients with diabetes,¹⁶ those with chronic kidney disease,¹⁷ those suffer-

Table 2 | Drug interactions with ticagrelor^{9,13}

Interacting drug	Effect of Interaction on ticagrelor	Recommendation
Strong CYP3A4 Inhibitors (clarithromycin, ketoconazole, ritonavir, atazanavir, and nefazodone)	↑ C_{max} 240%, ↑ AUC 730%	Avoid concomitant use
Moderate CYP3A4 Inhibitors (diltiazem, amprenavir, fluconazole, erythromycin, and aprepitant)	↑ C_{max} 69%, ↑ AUC 174%	No dose adjustment
Potent CYP3A4 Inducers (dexamethasone, rifampin, carbamazepine, phenytoin, and phenobarbital)	↓ C_{max} 73%, ↓ AUC 86%	Avoid concomitant use
Interacting drug	Effect of Interaction on co-administration drug	Recommendation
P-gp substrates (digoxin, cyclosporine)	↑ C_{max} 75%, ↑ AUC 28%	Appropriate monitoring
Simvastatin	↑ C_{max} 81%, ↑ AUC 56%	Avoid concomitant use with simvastatin or lovastatin doses > 40 mg

AUC= area under the plasma concentration- time curve; C_{max} = maximum plasma concentration

Table 3 | Summary of major ticagrelor clinical trials in patients with acute coronary syndrome ^{7, 14, 15, 16, 20, 21}

Trial	Design	Outcomes	Intervention	Results
DISPERSE-2 ¹⁴ (2007)	Duration: 4- 12 weeks N= 990 R, MC, DB, DD	Rate of bleeding: Major bleeding Minor bleeding	TGR 90 mg BID +ASA TGR 180 mg BID +ASA CPL 300 mg LD, 75 mg QD + ASA	No significant difference between the 3 treatment groups for major bleeding. More minor bleeding with TGR 180 mg BID (6.1%) vs CPL (1.3%, P=0.01)
PLATO ¹⁵ (2009)	Duration: 1 year N= 18,624 R, MC, DB, DD, PG	Efficacy: rate of death from vascular causes, MI, stroke Safety: any major bleeding event	TGR 180 mg LD, 90 mg BID + ASA CPL 300 mg LD, 75 mg QD + ASA	Primary efficacy endpoint occurred 11.7% in CPL group vs 9.8% in TGR group (HR: 0.84; [CI] 0.77- 0.92; P<0.001). Primary safety end point showed no difference in rates of major bleeding in TGR vs CPL (11. 6%, 11.2%, respectively; P= 0.43).
PLATO-DM ¹⁶ (2010)	Duration: 6-12 months N= 4662 DM pts Mean A1c: 6% Retrospective, R, MC, DB, DD, PG	Efficacy: rate of death from vascular causes, MI, stroke Safety: any major bleeding event	TGR 180 mg LD, 90 mg BID + ASA CPL 300 mg LD, 75 mg QD + ASA	Primary efficacy endpoint: In pts w/ DM treated w/ TGR reduction in primary composite endpoint (HR:0.88; [CI] 0.76- 1.03), all-cause mortality (HR: 0.82; [CI] 0.66- 1.01), stent thrombosis (HR: 0.65; [CI] 0.36- 1.17). Safety: No increase in major bleeding with TGR (HR: 0.95; [CI] 0.81- 1.12)
PLATO-CABG ²⁰ (2011)	Duration: 1 year N= 1,899 pts underwent CABG Retrospective, R, DB, DD	Primary efficacy endpoint: time from CABG to first occurrence of any event from the composite of death from vascular causes, MI, or stroke. Primary safety endpoint: time from CABG to the first occurrence of any major bleeding event	All pts were receiving study drug treatment <7 days before surgery TGR/placebo be withheld for 24- 72 hrs pre-op CPL/placebo be withheld for 5 days pre-op	Efficacy: Relative reduction of primary composite endpoint-TGR: 66/ 629 (10.6%) vs CPL 79/629 (13.1%) with (HR: 0.84; [CI] 0.60- 1.16; P= 0.29). Safety: NS difference in CABG- related bleeding between randomized treatments
ONSET/OFFSET ⁷ (2009)	Duration: 6 weeks N= 123 R, MC, DB, DD, PG	Primary endpoint: Onset, IPA after 2 hrs of LD Offset, IPA at the end of 6 weeks of treatment	TGR 180 mg LD, 90 mg BID + ASA CPL 600 mg LD, 75 mg QD	Primary endpoints: Onset: IPA was greater for TGR than CPL at 2 hours (88% vs 38%, P<0.0001). Offset: IPA was higher in TGR vs CPL (P<0.0001).
RESPOND ²¹ (2010)	N= 98 R, DB, DD, two- way crossover	Primary outcome: proportion of CPL NR who responded to TGR based on IPA 4 h after last dose	CPL 600 mg LD, 75 mg QD + ASA TGR 180 mg LD, 90 mg BID + ASA	Primary outcome: IPA higher in NR treated w/ TGR compared w/ CPL (P<0.05) .

ASA= aspirin; BID= twice a day; CABG= coronary artery bypass graft; [CI]= 95% confidence interval; CPL= clopidogrel; DB= double- blinded; DD= double- dummy; DM= diabetes mellitus; IPA= inhibition of platelet aggregation; LD= loading dose; MC= multi-center; MI= myocardial infarction; NR= nonresponder; NS= not statistically significant; PG= parallel-group; QD= once daily; R= randomized; TGR= ticagrelor.

ing from an ST-elevation ACS,¹⁸ those undergoing a planned invasive strategy for ACS,¹⁹ and those undergoing coronary artery bypass surgery (CABG).²⁰ Results from subgroup studies were generally the same as those in the parent PLATO trial in terms of clinical efficacy and major bleeding rates. **Table 3** summarizes the major ticagrelor clinical trials in patients with ACS.

However, one subgroup analysis of the PLATO data suggested that patients enrolled in the trial from the United States (n= 1413) fared worse with ticagrelor compared with clopidogrel (U.S. patients: HR: 1.27, P= 0.146; non- U.S patients: HR: 0.91, P< 0.0001).²² Results of two independently performed analyses identified an underlying statistical interaction with aspirin maintenance dose as a possible explanation for the regional difference. The lowest risk of cardiovascular death, MI, or stroke with ticagrelor compared with clopidogrel is associated with a low maintenance dose of concomitant aspirin. It is important to note that subgroup analysis is not confirmatory, only hypothesis generating, so these results should be interpreted cautiously.

ADVERSE EVENTS

Ticagrelor was generally well tolerated in patient with ACS in the PLATO trial (**Table 4**).¹⁵

As a class, the signature adverse event associated with P2Y₁₂ receptor antagonists is bleeding.^{9,15} Over 12 months of therapy, no significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P= 0.43). However, ticagrelor was associated with a higher rate of non-CABG- related major bleeding (4.5% vs 3.8%, P=0.03). With ticagrelor compared to clopidogrel, there were more episodes of intracranial bleeding (26/9235 patients [0.3%] vs 14/9186 patients [0.2%]; P=0.06), including more instances of fatal intracranial bleeding (11/9235 patients [0.1%], 1/9186 patients [0.01%]; P= 0.02).

Dyspnea was more common in the ticagrelor group than in the clopidogrel group (13.8% vs 7.8%; P<0.001).^{9, 23, 24} In general, dyspnea symptoms were mild to moderate in severity and were reported soon after treatment initiation as a solitary episode, with some episodes (~30%) resolving in 7 days.⁹ The dyspnea associated with ticagrelor is thought to be related to increased adenosine concentrations activating the A₁ receptor.^{9, 15, 23, 24} As a precursor of adenosine, ticagrelor loses propyl sulfate and benzodifluoride residuals after oral digestion, ultimately increasing blood adenosine content.²⁴

Ticagrelor causes mild increases in serum uric acid (0.6 mg/dL increase compared with 0.2 mg/dL with

clopidogrel), although the clinical significance has not been fully elucidated.⁹ The proposed mechanism of increase in serum uric acid is increased adenosine concentrations stimulating the A_{2A} receptor, which causes upregulation of purine metabolism and inhibition of uric acid transport. Uric acid is the final metabolic product of adenosine which ticagrelor has been shown to increase. The frequency of gout (0.6%) was low and not significantly different between groups.^{9, 15, 24}

SAFETY ISSUES

The FDA has issued a number of boxed warnings for ticagrelor due to an increased risk of significant, sometimes fatal bleeding.⁹ Ticagrelor is contraindicated in patients with active pathological bleeding or a history of intracranial hemorrhage.^{9,15} When possible, discontinue ticagrelor at least 5 days prior to any elective surgery. Maintenance doses of aspirin greater than 100 mg/day may reduce the efficacy of ticagrelor and should be avoided.^{9, 15, 22}

In addition to a boxed warning, the FDA requires a risk evaluation and mitigation strategy (REMS) for ticagrelor.⁹ The REMS consists of a medication guide for patients, a communication plan for health care providers, and a plan to assess the effectiveness of the REMS program.

Table 4 | Adverse events in the PLATO trial.^{9,15}

Adverse Event	Ticagrelor 90 mg BID (N= 9235)	Clopidogrel 75 mg QD (N=9186)
Dyspnea ^a	1270 (13.8 %)	721 (7.8 %)
Headache	600 (6.5%)	532 (5.8 %)
Cough	452 (4.9%)	422 (4.6%)
Dizziness	415 (4.5%)	358 (3.9%)
Major bleeding	961 (11.6%)	929 (11.2%)
Life-threatening bleeding or fatal bleeding	491 (5.8%)	480 (5.8%)
Non-CABG- related bleeding ^b	362 (4.5%)	306 (3.8%)
Intracranial bleeding	26 (0.3%)	14 (0.2%)

^a Significantly more dyspnea with ticagrelor compared to clopidogrel (p<0.001).

^b Significantly more non-CABG- related bleeding with ticagrelor compared to clopidogrel (p=0.03).

BID= twice a day; CABG= coronary artery bypass graft; QD= once daily

DOSING AND ADMINISTRATION

Treatment with ticagrelor for ACS should begin with a loading dose of 180 mg followed by 90 mg twice daily taken without regard to meals.⁹ Aspirin should be coadministered with ticagrelor, unless contraindicated. After an initial aspirin dose of 325 mg, the recommended aspirin maintenance dose is 75-100 mg/day. Patients can be switched from clopidogrel to ticagrelor. Clinicians should administer the first 90 mg dose of ticagrelor 24 hours following the last dose of clopidogrel. Duration of treatment with ticagrelor should be continued for up to 12 months, unless clinically indicated. As with other antiplatelet therapies, premature discontinuation may increase the risk of MI, stent thrombosis, and death.⁹

Ticagrelor is not advised for use in patients on renal dialysis and is contraindicated in patients with severe hepatic impairment.^{9, 12, 17}

COST

The average monthly retail cost of ticagrelor approaches \$262, with a daily cost of \$8.71 (Table 5).

The cost-effectiveness of ticagrelor compared to clopidogrel was evaluated in a pharmacoeconomic study, which demonstrated a reduction in 1-year of health care utilization costs of \$977.00 per patient with ticagrelor compared to clopidogrel, including fewer intensive care unit days and shorter hospital lengths of stay.²⁵

PLACE IN THERAPY

Current European Society of Cardiology (ESC) guidelines recommend ticagrelor for all non-ST elevation ACS patients at moderate-to-high risk of ischaemic events, regardless of initial treatment

Table 5 | Average retail cost of ticagrelor vs. clopidogrel per month^a

Product	Average Price	Range
Brilinta® (ticagrelor) 90 mg Qty: 60	\$261.58	\$252.99- \$274.95
Plavix® (clopidogrel) 75 mg Qty: 30	\$211.18	\$198.99- \$220.97

^a Survey of chain, independent, discount, and grocery-store retail pharmacy prices (n=6) located in Gainesville, Florida as of September 2011.

strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) (Class 1, level of evidence B).²⁶ In addition, the guidelines recommend ticagrelor be considered for initiation or resumption following (CABG) surgery as soon as it is considered safe (Class IIa, level of evidence B). Since ticagrelor is reversible, it does not have to be withheld for 5 to 7 days prior to CABG like clopidogrel.²⁰

The 2011 ESC guidelines are more current than the American College of Cardiology (ACC)/American Heart Association (AHA) unstable angina/non-STEMI guidelines released earlier this year, when ticagrelor was not yet on the market and therefore no recommendation on the use of ticagrelor was provided.²⁶ Future ACC/AHA guidelines are expected to include a recommendation on the use of ticagrelor.

SUMMARY

Ticagrelor belongs to a new class of antiplatelets, cyclopentyl- triazolo- pyrimidines, and is the first oral antagonist of the P2Y₁₂ receptor that binds to the receptor reversibly. In contrast to clopidogrel, ticagrelor does not require metabolic activation. Ticagrelor avoids the variability seen with the CYP450 system and therefore produces a consistent antiplatelet effect. Ticagrelor provides greater platelet inhibition with a faster onset and offset of action than clopidogrel. The superiority of ticagrelor over clopidogrel with regard to the primary end point, composite of vascular death, MI, and stroke, as well as the similarity in rates of major bleeding, indicates a promising option for the treatment of patients with ACS. However, the FDA has issued boxed warnings and REMS as a part of the approval process for ticagrelor. Ticagrelor is dosed at 90 mg twice daily. The economic advantages of ticagrelor may be mitigated with the availability of generic clopidogrel, which is expected in May 2012.

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CLINICAL TRIAL UPDATE

2011 J Am Soc Neph — Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD¹ | Authors randomized 661 patients with hypertension (HTN) to take all of their HTN medications upon awakening in the morning or to take ≥ 1 HTN medication at bedtime. Patients had to have been ≥ 18 years old, have a diagnosis of HTN (based on ambulatory blood pressure monitoring [ABPM] criteria: an awake mean blood pressure [BP] $\geq 135/85$ mmHg or a mean asleep BP $\geq 120/70$ mmHg), and a diagnosis of chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min, albuminuria defined as ≥ 30 mg/24-hour urine), or both. Pertinent exclusion criteria included pregnancy, night- or shift-work employment, type 1 diabetes, secondary HTN, or cardiovascular disease (CVD) (i.e. unstable angina, heart failure, atrial fibrillation, kidney failure, or grade III-IV retinopathy). Baseline characteristics were similar between groups for both HTN medications, laboratory parameters, and BP parameters.

Patients underwent 48-hour ABPM at least annually or 3 months after any change in treatment; clinic BP was also measured and recorded as the average of 6 conventionally measured BPs prior to starting 48-hour ABPM. The primary outcome, CVD morbidity and mortality, was the composite of all-cause mortality, myocardial infarction (MI), angina, coronary revascularization, heart failure, acute arterial occlusion of lower extremities, thrombotic occlusion of the retinal artery, hemorrhagic stroke, ischemic stroke, and transient ischemic attack (TIA). Secondary outcomes included: major CVD events, defined as the composite of CVD-related death, MI, and stroke.

After a median follow-up of 5.4 years, a total of 139 primary outcome events were recorded. Patients who took ≥ 1 HTN medication at bedtime had a reduced rate of the primary outcome compared to those who took all of their HTN medications upon awakening (HR 0.31; 95% Confidence Interval [CI] 0.21-0.46; $p < 0.001$, adjusted for sex, age, and diabetes status). Also, patients taking ≥ 1 HTN medication at bedtime had a reduced rate of major CVD events (HR 0.28; 95% CI 0.13-0.61; $p < 0.001$, adjusted for sex, age, and diabetes status).

The authors found that patients who took ≥ 1 HTN at bedtime exhibited significantly better sleep-time BP control, although awake BP control did not differ between groups. Cox regression analyses (using the change in BP during follow-up as a time-dependent covariate, and adjusted for sex, age, diabetes, number of HTN medications, and baseline BP) showed that a decrease in mean asleep systolic blood pressure (SBP) was most significantly associated with event-free survival (HR 0.86; 95% CI 0.77-0.96; $p < 0.001$, for every 5 mmHg decrease in mean asleep SBP); the decrease in mean awake SBP was not associated with event-free survival (HR 0.95; $p = 0.247$).

A J-curve relationship to blood pressure and cardiovascular risk has been reported such that as BP is re-

duced, CVD risk is also reduced until a certain BP is attained at which point any further reduction in BP increases the risk for CVD. In the present study this relationship was seen for achieved clinic BP: the lowest quintile had a higher risk for CVD events (mean BP 122.3 mmHg) compared to second lowest quintile (mean SBP 137.1 mmHg). This J-curve relationship was not observed for mean asleep SBP and the authors suggest the J-curve relationship seen with the clinic BP may not exist for asleep BP, as long as nocturnal hypotension can be avoided. Lack of a J-curve for mean asleep SBP suggests that there is not a threshold at which point the benefits of BP reduction are attenuated, a threshold which does appear to exist for mean clinic SBP. Significantly more patients in the group taking ≥ 1 HTN medication at bedtime also had a decline of $> 10\%$ in sleep-time SBP (so called “dippers”) (59% vs. 28.9%, $p < 0.001$).

Treatment also showed a benefit on CKD parameters. For those taking ≥ 1 HTN medication at bedtime, eGFR was unchanged compared to a slight reduction in those taking all of their HTN medications upon awakening (1.9 mL/min between group difference, $p = 0.043$). Bedtime treatment was also associated with a greater percent reduction of albumin excretion (26.9% vs. 15.6%, $p = 0.018$).

In conclusion, for patients with HTN and CKD who take multiple blood pressure medications, taking at least one HTN medication at bedtime reduces the risk for cardiovascular events and improves BP control as compared to taking all HTN medications upon awakening.

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