Diltiazem extended-release tablets (Tiazac® XC) in the treatment of hypertension

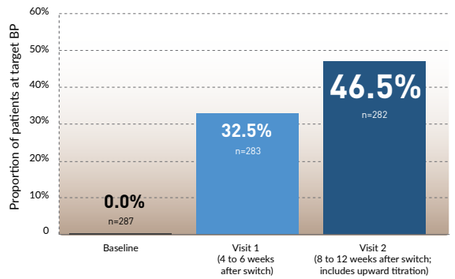
In line with the anticipated efficacy of diltiazem, this formulation has been shown to provide significant reductions in 24-hour SBP and DBP. This effect was particularly pronounced during the morning hours of 6 AM to 12 NOON, where a 12.0 mmHg and 9.9 mmHg reduction was seen in SBP and DBP, respectively.

"Non-dihydropyridine CCBs like diltiazem are effective therapies for the control of angina, atrial arrythmias and hypertension and continue to play an important role in CV risk reduction."

Dr. A. Shekhar Pandey

In a real-world study of patients with mild to moderate hypertension, diltiazem extended-release tablets were found to provide a median morning systolic BP reduction of 15 mmHg in patients previously uncontrolled on other diltiazem formulations. Approximately half of the patients switched to diltiazem extended-release tablets achieved target BP within 8 to 12 weeks.

Percent of patients reaching target BP after being switched from another diltiazem formulation to an equivalent dose of diltiazem hydrochloride extended-release tablets



Adapted from Fitchett DH et al. (2006) American Journal of Cardiovascular Drugs.

Important dosing considerations for antihypertensives

In the past, there has been a general underdosing of all antihypertensives, including diltiazem formulations. Data on CV risk reduction with most antihypertensives have come from moderate to high dose of those agents. CV risk reduction data with low or starting dose of antihypertensives is often lacking. When using diltiazem extended-release tablets, for example, as monotherapy in the treatment of hypertension, the usual starting dose should be 180 to 240 mg once daily at nighttime, with dosage adjustments every 2 to 4 weeks up to a **maximum of 360 mg**. This upward titration is important in patients sub-optimally controlled at lower doses, because while higher doses may not result in a greater anti-angina effect, they will have a greater anti-hypertensive effect and can help patients achieve their target BP.

Key clinical considerations for the use of calcium channel blockers in hypertension:

When to consider diltiazem extended-release tablets in your practice:

- Hypertension patients experiencing an exaggerated morning BP surge
- Hypertension patients not well controlled on alternative monotherapy
- Hypertension patients with diabetes
- Hypertension patients with proteinuria
- Patients with chronic stable angina
- Coronary artery disease patients with hypertension and stable angina pectoris but without prior heart failure, heart attack, or coronary artery bypass surgery
- Patients with atrial fibrillation or atrial arrythmias but without heart failure or left ventricular dysfunction

On the other hand, because of their effect on heart rate, non-DHP CCBs should be avoided in patients with heart failure, left ventricular dysfunction, heart block, bradycardia or when patients are on other rate-lowering agents like B-Blockers or Amiodarone. In general, all vasodilating agents, like CCBs, should be avoided with significant aortic stenosis.

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New 2016 CHEP guidelines are now available

The Canadian Hypertension Education Program (CHEP) Guidelines Task Force works to annually update Hypertension Canada's clinical practice guidelines for blood pressure management, diagnosis, assessment of risk, prevention, and treatment of hypertension. Within the 2016 guidelines update, an important new recommendation was added based on new study findings that aim to reduce the risk of cardiovascular events in select high-risk patients.

Traditionally, the treatment goal for non-diabetic hypertensive patients has been to achieve a systolic blood pressure (SBP) of <140 mmHg and a diastolic blood pressure (DBP) of <90 mmHg. However, the recently released SPRINT trial has now demonstrated that a more aggressive SBP goal of <120 mmHg should be considered for patients at a high risk for coronary artery disease complications, as this was shown to result in lower rates of fatal and nonfatal major cardiovascular events and death from any cause. In fact, the clinical study was terminated after only 3.26 years as significant results were seen before the end of the planned 5 years of follow-up. Based on these findings, the CHEP guidelines now recommend taking an intensive management approach in high-risk patients aged 50 years and older.

CURRENT UPDATES IN HYPERTENSION MANAGEMENT:

Taking a closer look at new studies and important changes to the CHEP hypertension guidelines.

CHEP 2016 Update:
For high-risk patients, aged ≥50 years, with systolic BP levels ≥130 mmHg, intensive management to target a systolic BP ≤120 mmHg should be considered. Intensive management should be guided by automated office BP measurements.

For the full CHEP publication, please visit:
http://guidelines.hypertension.ca/chep-resources/

In order to achieve these more aggressive SBP goals, it is recommended that clinicians follow up with their patients on a monthly basis until target BP levels are achieved as per the SPRINT trial protocol. On average, 2.7 medications were required to achieve target BP with intensive management, so it is important to consider the use of multiple treatment options in patients within your clinic. Use the CHEP guidelines to select medications that will work well together within each individual patient.

"In my experience and my reading of the literature, it is suggested that an ACE-i or ARB as a first-line option followed by the addition of a CCB are often great initial therapeutic options. At that point, I often add a low-dose diuretic. Chlorthalidone is often the diuretic I turn to as it is a longer-acting diuretic and may have persistent blood pressure lowering effects. Chlorthalidone also has the most robust data for CV risk reduction of any diuretic available."

Dr. A. Shekhar Pandey

2016 CHEP Recommended Treatment Targets

Patient Population	SBP Target	DBP Target
High Risk • CKD • Elderly ≥75 years • CVD; FRS >15%	≤120 mmHg	N/A
Diabetes	<130 mmHg	<80 mmHg
All other hypertension patients	<140 mmHg	<90 mmHg

CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease (clinical or subclinical); FRS: Framingham Risk Score.

"The SPRINT study was a landmark study that has the potential to dramatically change the management of hypertension in Canada. If implemented effectively, it has the potential to significantly reduce the risk of stroke, congestive heart failure, and other cardiovascular end organ damage. It will require a lot of work, however, since it will likely mean most hypertensive patients may require 1 or more additional antihypertensives and the attendant need for close supervision."

Dr. A. Shekhar Pandey

The role of calcium channel blockers in the treatment of hypertension

CHEP 2016 Update:
CCBs are now also recommended as an option for the initial treatment of coronary artery disease (CAD) patients with hypertension and stable angina pectoris (without prior heart failure, heart attack, or coronary artery bypass surgery).

Calcium channel blockers (CCBs) are an effective treatment option

CCBs have been used for over 20 years in the treatment of mild to moderate hypertension, and long-acting formulations are a recommended first-line option in patients without other compelling indications for a specific agent. CCBs are also recommended for use in patients with certain compelling indications, such as those with diabetes, stable angina, recent heart attack (if beta-blockers are contraindicated or ineffective), heart failure, and left ventricular hypertrophy.

CCBs can be divided into two subclasses, non-dihydropyridines and dihydropyridines. Each class has different pharmacological effects within the body based on their interaction with separate areas of calcium ion channels. Please see below for the key differences between these two subclasses:

	Non-dihydropyridine CCBs	Dihydropyridine CCBs
Molecule	• Diltiazem (Cardizem® CD, Tiazac®, Tiazac® XC) • Verapamil (Verelan®)	• Amlodipine (Norvasc®) • Nifedipine (Adalat® XL®) • Felodipine (Plendil®)
Action site	Mainly the myocardium and cardiac conductive tissues	Mainly the peripheral vascular smooth muscle
Clinical effect	• Vasodilation • Reduction in blood pressure • Reduction in heart rate	• Vasodilation • Reduction in blood pressure
Tolerability	• Comparatively lower rates of edema • Significant reduction in proteinuria • Potential to cause cardiac conduction disturbances • Very few cases of severe bradycardia and conduction abnormalities have been reported in patients with uncomplicated hypertension	• Comparatively higher rates of edema • Minimal, if any, impact on proteinuria • Comparably higher rates of headache

"While both DHP and non-DHP CCBs have an important role to play in hypertension management and CV risk reduction, in specific patient populations like CAD patients and those with atrial arrythmias or atrial fibrillation, non-DHP CCBs may be especially effective."

Dr. A. Shekhar Pandey

Evolution of diltiazem hydrochloride

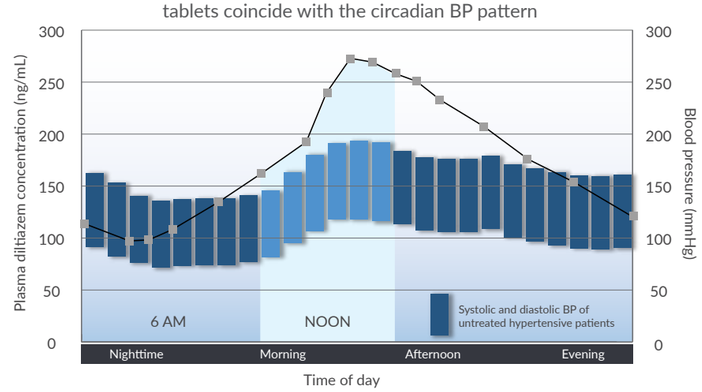
The non-dihydropyridine CCB diltiazem has been available for over 30 years and effectively treats both **mild to moderate hypertension and chronic stable angina**. The formulation of diltiazem has changed and evolved multiple times over the years in order to optimally manage these conditions.

The latest evolution of diltiazem (diltiazem extended-release tablets; Tiazac® XC) was designed using a delivery technology that complements the natural diurnal pattern of blood pressure (BP) and ensures plasma levels peak in the morning hours when taken at bedtime. This feature is unique to diltiazem extended-release tablets, as other sustained-release formulations of diltiazem do not demonstrate this effect, even when taken at nighttime.

This peak in plasma concentration coincides with the **morning BP surge**, which is the rapid and sharp increase in BP that occurs when a patient awakes and arises from bed. While it is referred to as the morning BP surge, it can occur at whatever time of day a patient typically wakes up.

This exaggerated rise in BP has been associated with an **increased cardiovascular risk and target organ damage** that is independent of a patient's 24-hour BP. As a result, the early morning hours after 6 AM when BP spikes are associated with an increased incidence in the onset of cardiovascular events.

Plasma concentration of diltiazem extended-release tablets coincide with the circadian BP pattern



Adapted from the Tiazac XC Product Monograph and Kario K (2010) Hypertension.

The morning BP surge has been associated with an increased risk of:

Stroke	Heart attack	Sudden cardiac death
46% *increase*	**40%** *increase*	**29%** *increase*

Given these risks, it is important to take the morning BP surge into consideration and tailor treatment in the appropriate patients to maintain control throughout the morning hours. Long-acting antihypertensives, like extended-release diltiazem, when taken in the evening may help to blunt and reverse the morning BP surge. It remains to be determined if this reduces the increased CV risk associated with the morning BP surge. In general, most antihypertensives, except for diuretics, should be taken in the evening to reduce nocturnal and early AM blood pressure abnormalities.

"ABPM provides a great deal of information to ensure adequate 24-hour control and can help guide dose adjustments, selection of medication timing, adjustments to longer-acting agents to avoid the early morning surge, and the potential need for additional therapies. We are also learning that there is a significant percent of the population that has 'masked' or 'reverse white-coat' hypertension, where blood pressure is actually lower in the clinic setting than at home. As well, ABPM can help identify a lack of nocturnal dip or rise in blood pressure nocturnally that can significantly increase the risk of congestive heart failure, renal failure, and stroke. It can also help identify patients that may have sleep-disordered breathing, like sleep apnea, where intervention for these conditions can help reduce cardiovascular risk."

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CHEP 2016 Update:
The 2016 CHEP guidelines now recommend using out-of-office measurements [24-hour Ambulatory Blood Pressure Monitoring (**ABPM**)] or home BP readings to confirm the initial diagnosis in any individual suspected of having hypertension. ABPM is also an important tool in identifying an exaggerated morning BP surge in your patients, as it provides measurements in the hours before and after awaking.