Medications and Falls
Part - 1
Introduction with General Principles and Risk Evaluation for Cardiovascular Medications

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Saint Francis Hospital and Medical Center
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December 14, 2018

Learning Objectives:
1. Review the epidemiological data on falls and the elderly.
2. Discuss some general principles as they apply to an analysis of medication use and falls.
3. Review the various classes of antihypertensive medications and their relative risk for causing falls in the elderly.
4. Define postural hypotension, discuss the physiological mechanisms for upright blood pressure control and explain how medications can compromise these mechanisms.
5. Discuss some cases of medication-induced falls related to the use of antihypertensive medications or medications with secondary blood pressure lowering effects.

Some Facts

Centers for Disease Control (CDC)
Falls Statistics for Older Adults (≥65yrs)
• During 2014 approximately 27,000 older adults died because of falls.
• Nearly 3 million older adults were treated in the ED for fall-related injuries, including fractures and head trauma, and about 800,000 of these patients required hospitalization.
Medicare currently will not pay to treat an injury resulting from a fall in in a hospital.

Summary
What is already known about this topic?
Falls are the leading cause of fatal and nonfatal injuries among persons aged 65 years and older adults.
What is added by this report?
In 2014, 28.7% of older adults reported falling at least once in the preceding 12 months, resulting in an estimated 2.9 million falls. Of those who fell, 37.5% reported at least one fall that required medical treatment or restricted their activity for at least 1 day, resulting in an estimated 7.9 million fall injuries.
What are the implications for public health practice?
Although falls are common, approximately half of older adults who fall do not discuss it with their healthcare provider, however, older adult falls are largely preventable.

Healthcare providers can play an important role in fall prevention by:
1) screening older adults for fall risk,
2) reviewing and managing medications linked to falls, and
3) recommending vitamin D where appropriate for improved bone, muscle, and nerve health.

Some Other Important Adverse Events

Appendix B. Counts of Adverse Event Codes 2012-2017 (half year)

<table>
<thead>
<tr>
<th></th>
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<td>CT 1</td>
<td>Paternal death or severe injury as a result of organ failure</td>
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<td>02</td>
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<td>Paternal death or severe injury as a result of organ failure</td>
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<td>05</td>
<td>05</td>
<td>06</td>
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<tr>
<td>NQF 64</td>
<td>Medication errors</td>
<td>06</td>
<td>07</td>
<td>08</td>
<td>09</td>
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</tbody>
</table>

Appendix A: Connecticut Adverse Events in 2018

Most Frequently Reported Events

<table>
<thead>
<tr>
<th>Event Code</th>
<th>Descriptions</th>
<th>Frequency</th>
<th>Percent of AD/Events</th>
</tr>
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<tbody>
<tr>
<td>CT 1</td>
<td>Paternal death or severe injury as a result of organ failure</td>
<td>00</td>
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<tr>
<td>CT 2</td>
<td>Paternal death or severe injury as a result of organ failure</td>
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<tr>
<td>NQF 64</td>
<td>Medication errors</td>
<td>06</td>
<td>07</td>
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Appendix C. Connecticut Adverse Events in 2016

Most Frequently Reported Events

NQF List (IA-7B) and Connecticut-Specific List (CT1 & CT2)

<table>
<thead>
<tr>
<th>Event Code</th>
<th>Descriptions</th>
<th>Frequency</th>
<th>Percent of AD/Events</th>
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</thead>
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<tr>
<td>11</td>
<td>Medication error: adverse reaction to medication</td>
<td>06</td>
<td>07</td>
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<tr>
<td>12</td>
<td>Medication error: adverse reaction to medication</td>
<td>08</td>
<td>09</td>
</tr>
<tr>
<td>13</td>
<td>Medication error: adverse reaction to medication</td>
<td>10</td>
<td>11</td>
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<td>14</td>
<td>Medication error: adverse reaction to medication</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>15</td>
<td>Medication error: adverse reaction to medication</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

Appendix D. Adverse Event Reports by Event Type

Acute Care Hospitals - Connecticut (2015)
In 2016 there were 285 fall-related SREs in Mass vs 74 events in CT
Falls and Medications

Traditional Risk Factors for Falls

- Cognitive impairment
- Stroke history
- History of falls
- Failed “Get up and go test” (decreased proximal muscle strength)
- Walking difficulty – gait/balance or arthritis
- Visual impairment
- Postural hypotension (Orthostasis)
- Urinary incontinence
- Selected medications or Polypharmacy

Some pharmacology principles related to a fall investigation

Drug Administration And Clearance Issues
Peak plasma drug concentrations after oral administration occur in about 2 hours when fasted and later when fed.

Liquid preparations given in a fasted state can peak in 30 minutes.

Drug elimination phase

Clonidine plasma levels and effects on BP

Fig. 3. Mean plasma concentration of clonidine (upper panel) in 5 normal subjects who had an oral dose of 300 µg of clonidine with the mean change in their systolic blood pressure (—--), and diastolic pressure ( — — ). (Lower panel)

Flow of saliva, g/min

Fig. 4. Mean and standard error of mean flow of saliva in 5 subjects for 8 hr after 300 µg of clonidine by mouth.

Patient fell on 2-17-2010 at 00:15

Duloxetine 20 mg capsule DR

16 Feb 2010 21:11
Value: 40 mg
Facility: SFMH
Frequency: DAILY8P
Route: PO
Patient fell on 2-17-2010 at 00:15

Drug Administration And Clearance Issues

Standard doses of medications may produce more intense effects in the elderly

Drug → Liver → Metabolite

Young

Drug → Liver → Metabolite

Elderly

CREATININE CLEARANCE VS AGE IN WOMEN

CREATININE CLEARANCE VS AGE IN MEN
An acute change in renal function (AKI) may prolong the half-life of a medication, making it more toxic if a dosage adjustment is not done. A toxic effect may include gait and balance disturbances leading to a fall.

If a patient falls shortly after having an episode of AKI, check for a medication that should have been adjusted or stopped during that period.

For Many Medications Exaggerated Responses are Observed in the Elderly

- Sedative / hypnotics
- Blood pressure lowering agents
- Anticoagulants
- Antipsychotic medication
- Lithium
- Diuretics
- Anti-inflammatory drugs

Medication debridement is a key component to a falls reduction program

Consider

Discontinue or dosage reduction
Orthostatic Hypotension

Orthostatic Hypotension aka Postural Hypotension:
An adverse effect common with many medications

In order to standardize the assessment and diagnosis of orthostatic hypotension (OH), the American Autonomic Society and the American Association of Neurology define OH as a decrease in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg within 3 minutes of standing.

Miller and Appel, Circulation 2015

Patients in the following five categories need to be routinely screened for OH:

(1) Patients suspected of, or diagnosed with any neurodegenerative disorder associated with autonomic dysfunction, including Parkinson's Disease (PD), Multiple System Atrophy (MSA), Pure Autonomic Failure (PAF), or Dementia with Lewy Bodies (DLB);

(2) Patients who have reported an unexplained fall or have had an episode of syncope;

(3) Patients with peripheral neuropathies known to be associated with autonomic dysfunction (e.g., diabetes, amyloidosis, HIV);

(4) Patients who are elderly (≥70 years of age) and frail or on multiple medications;

(5) Patients with postural (orthostatic) dizziness or nonspecific symptoms that only occur when standing.
Upright posture
Venous pooling
Decreased cardiac output
Decreased blood pressure
Activation of baroreceptors
Stimulation of brainstem vasomotor center
Increased sympathetic outflow (norepi and epi)
Increase heart rate and force of contraction arteriolar and venous constriction
Increased blood pressure (maintained)

Principles of Blood Pressure Control in the Upright Position

Seated vs Supine

Blood Pressure and Falls

• Sustained hypotension

• Orthostatic hypotension

Cardiovascular Medications

Some General Comments

The Risk of Hip Fracture After Initiating Antihypertensive Drugs in the Elderly

Debra A. Rast, MD, MS, CCFP, FCAP; Mohammad Mamanpur, PharmD, MPH; Peter C. Austin, PhD; Karen Tu, MD, MS, CCFP, FCAP; Tara Gomes, MSc; Richard H. Gleicher, MD, MPH, CCFP, FCAP

Conclusions: Antihypertensive drugs were associated with an immediate increased hip fracture risk during the initiation of treatment in hypertensive community-dwelling elderly patients. Caution is advised when initiating antihypertensive drugs in the elderly.

Arch Intern Med. 2012;172(22):1739-1744
The Concept of Trade-offs in Health Outcomes

Use of antihypertensive medications in a patient with fall risks

- Increased risk of fall complications (fractures and TBI)
- Decreased CV complications (stroke, MI, HF)
- Medications-related symptoms (dizziness, fatigue)

*Fall in the previous year, use of a cane or walker, balance or walking difficulty, one or more ADL dependencies, postural hypotension, visual impairment, depressive symptoms, at least 4 meds

Tinetti, ME et al. JAGS 2008

Intensive vs standard blood pressure control

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Recommendation 1
In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.

Strong Recommendation – Grade A

JNC 8 | Published online December 18, 2013

Dosage adjustment was based on a mean of 3 blood pressure measurements at an office visit while the patient was seated and after 5 minutes of quiet rest. The measurements were made using an automated system (Omron Healthcare Model 907).
Orthostatic Hypotension
A drop in systolic blood pressure of at least 20 mm Hg or in diastolic pressure of at least 10 mm Hg at 1 minute after the patient stood up, as compared with the value obtained when the patient was seated.

Sprint Trial - NEJM November 26, 2015

### Serious Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Int Tx (%)</th>
<th>Std Tx (%)</th>
<th>Haz Ratio</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Hypotension</td>
<td>2.4</td>
<td>1.4</td>
<td>1.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>2.3</td>
<td>1.7</td>
<td>1.33</td>
<td>0.003</td>
</tr>
<tr>
<td>Lyte abn</td>
<td>3.1</td>
<td>2.3</td>
<td>1.35</td>
<td>0.02</td>
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<tr>
<td>AKI</td>
<td>4.1</td>
<td>2.5</td>
<td>1.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fall-Inj</td>
<td>2.2</td>
<td>2.3</td>
<td>0.95</td>
<td>0.71</td>
</tr>
</tbody>
</table>

NEJM November 26, 2015

### Classes of Cardiovascular Medications And Relative Fall Risk

- **Higher Risk**
  - Alpha Blockers
  - Beta Blockers
  - Diuretics (vol/dep, abn lyte)
  - Nitrates
- **Lower Risk**
  - ACEI
  - ARBs
  - CCB
  - K+ sparing diuretics

3 or more antihypertensive agents – high risk

### Alpha Blockers/Antagonists

- Alfuzosin (UroXatal)*
- Doxazosin (Cardura)
- Prazosin (Minipress)
- Terazosin (Hytrin)
- Tamsulosin (Flomax)*

Falls Associated ADE: postural hypotension, dizziness, weakness,

* Selective for the prostate gland
Tamsulosin (Flomax) = selective α antagonist

**Beta Blockers**
- Acebutolol (Sectral)
- Atenolol (Tenormin)
- Betaxolol (Kerlone)
- Bisoprolol (Zebeta)
- Carvedilol (Coreg)
- Labetalol (Trandate)
- Metoprolol (Lopressor)
- Nadolol (Corgard)
- Nebivolol (Bystolic)
- Pindolol (Visken)
- Propranolol (Inderal)
- Timolol (Blocadren)

Falls Associated ADE: bradycardia, fatigue, additive with other AHDs, OH-synergistic with alpha blockers

**Common Diuretics**

**Loop Type**
- Bumetanide
- Ethacrynic acid
- Furosemide
- Torsemide

**Thiazide Type**
- Chlorothiazide
- Chlorthalidone
- Hydrochlorothiazide
- Indapamide
- Metyclothiazide
- Metolozone

Falls Associated ADE: Volume and electrolyte abnormalities (K+ and Na+)

New loop diuretic prescriptions may be an acute risk factor for falls in the nursing home

Sarah D. Barry,1,2 Mary A. Mathews,1 Young Jueng,1 David H. Solomon,2 Louis A. Lipitz2
1Department of Rehabilitation Medicine, Case Western Reserve University and University Hospitals, Cleveland, OH; 2Department of Medicine, Case Western Reserve University and University Hospitals, Cleveland, OH

Results: During a mean follow-up of 4.3 months, 1317 participants experienced an incident fall. New participants experienced a diuretic change on the day before the fall. The odds of falling one day following a change in diuretics was elevated OR=1.58, 95% CI 1.09-2.28. We estimated that for every 270 loop diuretic drug changes, one extra fall occurred.

Conclusion: Nursing home residents are at an increased risk of fall in the day following a new prescription or increased dose of a loop diuretic drug. Early prescription should be taken immediately following a long diuretic drug change in excess to prevent falls. Copyright © 2012 BMJ Publishing Group Ltd

**Diuretics = Dehydration Orthostatic BP changes**
Furosemide Bolus vs Infusion Dosing

Chlorthalidone > Hydrochlorothiazide > Furosemide

Relative risk of hypokalemia or hyponatremia with daily dosing

Signs and Symptoms of Hyponatremia
- Acute presentation: early (125-130 mEq/L)-nausea and malaise; later (115-120 mEq/L)-headache, lethargy, obtundation, seizures, coma, respiratory arrest.
- Chronic presentation: fatigue, nausea, dizziness, gait disturbance (falls), forgetfulness, confusion, lethargy, muscle cramps

Signs and Symptoms of Hypokalemia
- Muscle: weakness ascending legs to trunk and arms that can progress to frank paralysis; muscle cramps, rhabdomyolysis, myoglobinuria; respiratory muscle weakness and GI involvement causing ileus
- ECG: ST segment depression, decreased T wave amplitude, increased U wave amplitude, and prolonged QT interval.
- Cardiac arrhythmias: Premature atrial and ventricular beats, sinus bradycardia, junctional tachycardia, AV block, and ventricular tachycardia/fibrillation.

Sodium (mEq/L)
- Hyponatremia <135
- Normonatremia 135-145
- Hypernatremia >145

Potassium (mEq/L)
- Hypokalemia <3.5
- Normokalemia 3.5 - 5.5
- Hyperkalemia >5.5

Figure 2. The mean hourly urine volumes. The open circles indicate the bolus group, and the closed circles indicate the infusion group. Asterisks indicate significant differences between the groups. (hour 5, p <0.01).
The Silent Epidemic of Thiazide-Induced Hyponatremia

Samuel J. Mann, MD

The risk of thiazide-induced hyponatremia is 3-fold higher in patients ≥70 years old and higher in women possibly because of smaller body size and lower sodium intake.

Common Nitrates

- Isosorbide dinitrate (Isordil)
- Isosorbide mononitrate (Imdur)
- Nitroglycerine (oint, TDD, spray, SL tabs)

Falls Associated ADE: Hypotension and postural hypotension (dizziness, lightheadedness) – probably most prevalent during pretolerance period.

Approximately 3 in 10 patients exposed to thiazide diuretics develop hyponatremia

Risk of Thiazide-induced Hyponatremia in Patients with Hypertension

Combinations of Cardiovascular Drugs That Have an Increased Risk for Hypotension

- Alpha blockers with beta blockers
- Three or more antihypertensive drugs
- Loop diuretics with metolozone
- Diuretics and ACEI (initiation)
- Amiodarone with clonidine
- Verapamil/Diltiazem with a beta blocker or clonidine

Cardiovascular Medications

- Higher Risk
  - Alpha Blockers
  - Beta Blockers
  - Diuretics (volume dep)
  - Nitrites

- Lower Risk
  - ACEI
  - ARBs
  - CCB
  - K+ sparing diuretics

3 or more antihypertensive agents – high risk
Angiotensin Converting Enzyme Inhibitors

- Benazepril (Lotensin)
- Captopril (Capoten)
- Enalapril (Vasotec)
- Fosinopril (Monopril)
- Lisinopril (Zestril)
- Moexipril (Univasc)
- Perindopril (Aceon)
- Quinapril (Accupril)
- Ramipril (Altace)
- Trandolapril (Mavik)

Falls Associated ADE: low incidence (dizziness, fatigue), mostly additive with other AHDs.

Angiotensin Receptor Blockers (ARBs)

- Candesartan (Atacand)
- Eprosartan (Teveten)
- Irbesartan (Avapro)
- Losartan (Cozaar)
- Olmesartan (Benicar)
- Telmisartan (Micardis)
- Valsartan (Diovan)

Falls Associated ADE: low incidence (dizziness, fatigue), mostly additive with other AHDs.

Calcium Channel Blockers

- Amlodipine (Norvasc)
- Diltiazem (Cardizem)
- Felodipine (Plendil)
- Isradipine (DynaCirc)
- Nicardipine (Cardene)
- Nifedipine (Procardia, Adalat)
- Nisoldipine (Sular)
- Verapamil (Isoptin)

Falls Associated ADE: low incidence (dizziness, fatigue), mostly additive with other AHDs.

Potassium Sparing Diuretics

- Amiloride (Midamor)
- Eplerenone (Inspra)
- Spironolactone (Aldactone)
- Triamterene (Dyrenium)

Falls Associated ADE: Hyperkalemia (conduction problems/bradycardia)

Hyperkalemia and Falls

- Muscle weakness
- Cardiac arrhythmias

Cases
76 y.o. man admitted for:
Near syncope

Table 2  Medications Frequently Associated with Falls by Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Agents</th>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Chlordiazepoxide, diazepam, alprazolam</td>
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<tr>
<td>Antidepressants</td>
<td>Amitriptyline, nortriptyline, fluoxetine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Risperidone, haloperidol, chlorpromazine, clozapine</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Phenytoin, phenobarbital</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Diphenhydramine, hyoscyamine, tolterodine, oxybutynin</td>
</tr>
<tr>
<td>Sedative hypnosis</td>
<td>All barbiturates, zolpidem, zaleplon</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Cyclobenzaprine, metaxalone, methocarbamol</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Diuretics, doxazosin, terazosin, clonidine, digoxin</td>
</tr>
</tbody>
</table>

American Journal of Medicine (2007) 120, 493-497

Tizanidine (first dose) given at 22:20 with terazosin, tramadol and metoprolol
Pulse low 90 minutes post med admin falling episode on 10/11 at 5:10 am
Low blood pressure x 3
Tizanidine = a clonidine derivative with issues of hypotension and bradycardia

Journal of Emergency Medicine - Apr 2011; Volume 44, Issue 4, Pages 415-420
Profound Symptomatic Bradycardia Requiring Transvenous Pacing After a Single Dose of Tizanidine
Hypotension and bradycardia associated with concomitant tizanidine and lisinopril therapy

SUSAN W. PURLOW AND DONALD L. BRANAN

Conclusion
The addition of tizanidine in a patient receiving long-term treatment with lisinopril was associated with severe hypotension and bradycardia.

Comments
- Pt with history of hypertension on background tx with beta blocker and alpha blocker was given 4 mg of the muscle relaxant tizanidine, a clonidine derivative know to cause bradycardia and hypotension. Reaction was temporally related to tizanidine administration.
- Not sure why this muscle relaxant with CV ADEs was chosen for a pt with background antihypertensive medications and an admitting dx of “near syncope”. Terazosin should be replaced by tamsulosin (Flomax®).

85 y.o. woman admitted to the CV service from the ED for syncope with falls. Discovered to be in AV block with bradycardia and hypotension.
Comment

- Very elderly woman with long history of syncope and falls at home.
- Found in ED to be in “heart block”.
- Patient orthostatic with symptoms in the ED.
- Home medications indicate excessive beta blockers, two as eye medications (timolol) and one oral (atenolol). Excessive beta blockage can produce AV block.

Another Case

76 y.o. / Man
Pt Loc: Medical-Tele Level 1
Patient Class: Inpatient
Admit Dx: BT (brain tumor) (HCC) [D49.6]
Admit Date: 09/30/2017
Allergies: Sulfas Antibiotics
Ht: 5’10” (1.778 m)
Wt (kg): 77.1 kg (170 lb)
Last BSA: 1.95 m² CrCl: 64.9 mL/min
Scr: 0.9 MG/DL

Home meds include 3 antihypertensive agents and insulin

Fall on 10/13 at 2:40
Comment

- Patient admitted to the hospital for evaluation of a newly diagnosed brain tumor. Of note this patient was hyponatremic on admission, hyponatremia being an important risk factor for falls and fractures.
- This patient was admitted on 3 antihypertensive medications - carvedilol, amlodipine and lisinopril. This burden of antihypertensive drugs places this patient at a high risk for syncope with falls.
- As an inpatient, chlorpromazine was initiated for hiccups. This medication is well recognized for causing significant orthostatic drops in blood pressure, effects that will be potentiated by co-prescribed antihypertensive medications.
- Description of in hospital fall is consistent with syncope.

Orthostatic changes in blood pressure noted day before fall on 10/12

Orthostatic changes noted 10 hrs post fall
Chlorpromazine discontinued

Upright posture
Venous pooling
Decreased cardiac output
Decreased blood pressure
Activation of baroreceptors
Stimulation of brainstem vasomotor center
Increased sympathetic outflow (norepi and epi)
Increase heart rate and force of contraction arteriolar and venous constriction
Increased blood pressure

CPZ-α antagonist
Beta blocker

Background treatment with 3 antihypertensive medications including a beta blocker (blocks reflex tachycardia) should have been considered when selecting a medication for hiccups
Multiple Choice Questions

1. In 2016 Connecticut Department of Public Health Report on serious hospital events, falls ranked as:
   a. The most common cause of death or injury.
   b. Second as a cause of death or injury.
   c. Third as a cause of death or injury.
   d. Almost equal to medication errors as cause of death or injury.

2. A consensus panel recommended screening for postural hypotension in all of the following patients except:
   a. Patients suspected of, or diagnosed with any neurodegenerative disorder associated with autonomic dysfunction
   b. Patients with peripheral neuropathies known to be associated with autonomic dysfunction
   c. Patients who are elderly (≥70 years of age) and frail or on multiple medications
   d. Patient’s with mild to moderate hypertension.

Multiple Choice Questions -continued

3. Which antihypertensive medication would NOT qualify as high risk for falls?
   a. Doxazosin
   b. Lisinopril
   c. Isosorbide dinitrate
   d. IV furosemide

4. Blood pressure measurements in the Sprint Trial (intensive treatment vs standard treatment) were done as follows:
   a. a single resting (1-3 minutes of rest) blood pressure determination
   b. average of 2 resting (1-3 minutes of rest) blood pressure measurements
   c. single measurement of both resting and standing blood pressure after 10 minutes of rest
   d. after 5 minutes of quiet rest, the average of 3 blood pressure determinations

5. Which non-antihypertensive medication has a high risk for hypotensive episodes?
   a. Diazepam
   b. Cimetidine
   c. Tizanidine
   d. Methocarbamol