高血壓、高血脂藥物臨床應用與案例討論

林口長庚醫院
新陳代謝科　臨床藥師
牛素珍

OUTLINE

- 高血壓、高血脂與心血管疾病的相關性
- 治療血壓及高血脂的重要性。
- 病例報告

Hypertension

Who should be treated

Introduction

- Treatment of hypertension generally begins with nonpharmacologic therapy, including moderate dietary sodium restriction, weight reduction in the obese, avoidance of excess alcohol intake, and regular aerobic exercise
- Drug therapy, in comparison, may be expensive and is often associated with side effects, some of which (hypokalemia and hyperlipidemia) may actually increase coronary risk
- Thus, there should be clear evidence of likely benefit before antihypertensive drugs are begun

Definitions

2003 by the seventh Joint National Committee (JNC 7)

reaffirmed by the American and International Societies of Hypertension (ASH/ISH) in 2014

- Normal blood pressure: <120 /80 mmHg
- Prehypertension: systolic 120 to 139 /or diastolic 80 to 89 mmHg
- Hypertension:
  - Stage 1: systolic 140 to 159 mmHg or diastolic 90 to 99 mmHg
  - Stage 2: systolic ≥160 mmHg or diastolic ≥100 mmHg
  - Isolated systolic hypertension: ≥140/<90 mmHg
  - Isolated diastolic hypertension : <140/≥90 mmHg

What Level of BP Increases Risk?

- Decreased cardiovascular risk with therapy

  Treatment studies have demonstrated the efficacy of lowering both diastolic and systolic pressures in patients with hypertension

  - Systolic and diastolic hypertension-
    - Low-risk patients : drug therapy is beneficial in patients who cannot control BP with lifestyle modification
  - Isolated systolic hypertension : SHEP trial (JAMA. 1991)
  - Isolated diastolic hypertension :
    - < 40 y/o, obese, The risk of cardiovascular complications appears to be lower with IDH than with SDH and ISH
  - Increased pulse pressure (SBP-DBP)
    - It has been suggested that there is an enhanced risk for cardiovascular events associated with increases in the pulse pressure

What Level of BP Increases Risk?

Goal blood pressure

- ESH/ESC guideline
  - All patients: < 140/90 mmHg
  - ≥ 80 y/o 150/90 mmHg
- JNC 8
  - < 60 y/o 140/90 mmHg
  - ≥ 60 y/o 150/90 mmHg
  - 60-79 y/o 140/90 mmHg (if it can be achieved without producing significant side effects)
  - In older patients with diabetes or chronic kidney disease, the blood pressure goal is <140/<90 mmHg

2015 Guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society(THS) for the Management of Hypertension

Blood pressure targets.

Categories	Targets (mmHg)	COR	LOE
Primary prevention	<140/90	IIa	B
Secondary prevention			
[redacted]		I	B
[redacted]		I	B
Stroke	<140/90	I	A
CKD	<140/90	I	A
[redacted]		IIb	C
Very elderly (age ≥80 years)	<150/90	IIa	B
[redacted]		I	B
antithrombotics for stroke prevention			

CHD: coronary heart disease; CKD: chronic kidney disease; COR: class of recommendation; LOE: level of evidence.

Treatment Recommendation

- All patients should undergo appropriate lifestyle (nonpharmacologic) modification
- < 60 y/o : Blood pressure persistently ≥140/90 mmHg
- 60-79 y/o : Blood pressure persistently ≥140 /90 mmHg
- 80 years and older : Blood pressure persistently ≥150/90 mmHg
- Starting with two drugs may be considered in patients with a baseline blood pressure more than 20/10 mmHg above goal
- In some patients with proteinuric chronic kidney disease or known cardiovascular disease, antihypertensive therapy may be indicated when the systolic pressure is persistently above 130 mmHg and/or the diastolic pressure is above 80 mmHg

Benefit of Treatment

- Early treatment of hypertension is particularly important in diabetic patients both to prevent cardiovascular disease and to minimize progression of renal disease and diabetic retinopathy

Choice of Antihypertensive Drugs

- Overall approach to selecting a therapy
  - Prevent mortality
  - Prevent adverse cardiovascular events, such as myocardial infarction, stroke, and heart failure
  - Prevent the progression of renal disease, if present
- ALLHAT trial
  - In the ALLHAT trial, diabetic patients had a significantly lower rate of new onset heart failure with low-dose chlorthalidone compared to amlodipine and lisinopril This effect may have been due at least in part to a lower attained blood pressure with chlorthalidone.

Choice of Antihypertensive Drugs

- Thiazide diuretics
  - Dietary salt restriction and low-dose thiazide diuretics are effective in hypertensive diabetic patients
  - Angiotensin-converting enzyme (ACE) inhibitors also may minimize or prevent some of the metabolic complications associated with diuretic therapy,(such as hypokalemia, hyperlipidemia and hyperuricemia)
  - Metabolic complications and a possible increase in cardiovascular risk have been a major concern with of diuretics in diabetic patients high doses
  - low-dose thiazide therapy minimizes the fall in plasma potassium concentration and the rise in triglyceride and uric acid concentrations in diabetic patients compared to higher thiazide doses

Choice of Antihypertensive Drugs

- Angiotensin inhibitors
  - ACE inhibitors —advantages
    - They lower the blood pressure,.
    - They have no specific toxicity, except for cough and raising the plasma potassium concentration in patients with underlying hyperkalemia or renal insufficiency
    - They have no adverse effects on lipid metabolism.
    - They may lower the plasma glucose concentration by increasing responsiveness to insulin
    - They protect against the progression of moderately increased albuminuria and severely increased albuminuria due to types 1 and 2 diabetes
    - They may slow the progression of retinopathy

Choice of Antihypertensive Drugs

- Angiotensin inhibitors
  - Angiotensin II receptor blockers
    - Angiotensin II receptor blockers (ARBs) appear to have the same benefits as ACE inhibitors described in the preceding section
    - Two major trials, the Irbesartan Diabetic Nephropathy Trial (IDNT) and the RENAAL trial, demonstrated a clear benefit in terms of renoprotection
- Combination renin-angiotensin system inhibition
  - do **not** recommend combination therapy with an ACE inhibitor and ARB or direct renin inhibitor

Choice of Antihypertensive Drugs

- Calcium channel blockers
  - Two relatively small initial trials suggested increased cardiovascular complications with nisoldipine or amlodipine compared to an ACE inhibitor
  - HOT and Syst-Eur, found no evidence of a deleterious effect from a long-acting dihydropyridine in diabetic patients
  - a **higher** rate of heart failure among diabetic patients was observed with amlodipine compared with chlorthalidone
  - Amlodipine may provide better protection against cardiovascular events than low-dose hydrochlorothiazide when both are used in combination with an ACE inhibitor

Choice of Antihypertensive Drugs

- Beta blockers
  - beta blockers are effective therapy for hypertension in diabetic patients
  - Carvedilol is a combined nonselective beta- and alpha-1 adrenergic antagonist that improves survival in patients with heart failure
    - GEMINI trial
      - (ACE inhibitor or ARB)→ randomly assigned to carvedilol, or metoprolol, or hydrochlorothiazide or dihydropyridine CCB were added as necessary to achieve a blood pressure below 130/80 mmHg
      - Carvedilol : No change in A1C , lower rate of progression to moderately increased albuminuria

Choice of Antihypertensive Drugs

- Alpha blockers
  - peripheral alpha blockers (such as doxazosin) are as effective in lowering blood pressure as ACE inhibitors and calcium channel blockers and have a more favorable metabolic profile
  - ALLHAT trial, the doxazosin arm was prematurely discontinued due to an increased rate of new onset heart failure compared to chlorthalidone
  - alpha blockers should **not** be used as primary therapy for hypertension

Choice of Antihypertensive Drugs

- Combination therapy and ACCOMPLISH
  - The primary endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death, and coronary revascularization
  - benazepril plus amlodipine better than benazepril plus low-dose hydrochlorothiazide

Choice of Antihypertensive Drugs

- Summary and Recommendations
  - An ACE inhibitor or ARB is preferred as initial therapy in a hypertensive diabetic patient
  - Monotherapy can attain goal blood pressure in some patients with diabetes and hypertension
  - combination therapy is eventually required in most patients. We suggest adding a long-acting dihydropyridine to the ACE inhibitor or ARB given the results of ACCOMPLISH
  - Other antihypertensive drugs can be added if the blood pressure goal is still not achieved
    - beta blocker is given-carvedilol
    - renal disease or heart failure--A loop diuretic is likely to be necessary

Hyperlipidemia management

Identification of Patients at Risk

- Lipid abnormalities are common in patients with diabetes mellitus, and undoubtedly contribute to the increase in risk of CVD
- The ADA recommends screening for lipid disorders at least annually in diabetic patients, and more often if needed to achieve goals.
- Adults with low-risk lipid values (LDL <100 mg/dL [2.6 mmol/L], HDL >50 mg/dL [1.3 mmol/L], and triglycerides <150 mg/dL [1.7 mmol/L]) may be screened every two years
- lifestyle intervention (diet, weight loss, increased physical activity) to improve the lipid profile in all patients with diabetes
- The initiation of statins is based upon cardiovascular risk rather than an LDL cholesterol level.

Drug therapy

- Statins
  - the only class of drugs to demonstrate clear improvements in overall mortality in primary and secondary prevention
- Nicotinic acid
  - a clinical trial of niacin suggested some mortality benefits in secondary prevention
- Large trials of cholestyramine, clofibrate, and gemfibrozil in primary prevention not only failed to show mortality benefits but showed worrisome trends toward an increase in noncardiac deaths

Drug therapy

- HMG-CoA Reductase Inhibitor (Statins)
- Nicotinic acid
- Cholesterol Absorption Inhibitor (Ezetimibe)
- Bile acid sequestrants (Cholestyramine)
- Fibrates

Guidelines for Management of Hypercholesterolemia

- The New Lipid Guidelines
  - Which were released on November 12, 2013, by the American College of Cardiology (ACC)/American Heart Association (AHA) guideline expert panel.

1. What's New in the Guideline

- *Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups*
  - 4 statin benefit groups were identified that focus efforts to reduce ASCVD events in secondary and primary prevention.
  - This guideline identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.
- *A New Perspective on LDL-C and/or Non–HDL-C Treatment Goals*
  - The appropriate intensity of statin therapy should be used to reduce ASCVD risk in *those most likely to benefit.*
  - Nonstatin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.

2.Overview of the Guideline

- Lifestyle as the Foundation for ASCVD Risk-Reduction Efforts
  - lifestyle modification (ie, adhering to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a crucial component of health promotion and ASCVD risk reduction
- Initiation of Statin Therapy
  - The Expert Panel found extensive and consistent evidence supporting the use of statins for the prevention of ASCVD in many higher-risk primary- and all secondary-prevention individuals without New York Heart Association class II–IV heart failure who were not receiving hemodialysis

3. Statin Treatment: Recommendations-1

- Intensity of Statin Therapy in Primary and Secondary Prevention
  - High-intensity statin therapy on average lowers LDL-C by approximately ≥50%, moderate-intensity statin therapy lowers LDL-C by approximately 30% to <50%, and lower-intensity statin therapy lowers LDL-C by <30%
- LDL-C and Non–HDL-C Treatment Goals
  - absence of data on titration of drug therapy to specific goals, no recommendations are made for or against specific LDL-C or non–HDL-C goals for the primary or secondary prevention of ASCVD

3. Statin Treatment: Recommendations-2

- Secondary Prevention
  - Women and men with clinical ASCVD
    - Age ≤75 years -> High-intensity statin therapy
    - Age >75 years -> moderate-intensity statin therapy

ASCVD : **AtheroSclerotic CardioVascular Disease**
Clinical ASCVD is defined by the inclusion criteria for the secondary prevention statin RCTs (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin)

3. Statin Treatment: Recommendations-3

- Primary Prevention in Individuals ≥21 Years of Age With LDL-C ≥190 mg/dL
  - high-intensity statin therapy to achieve at least a 50% reduction
- Primary Prevention in Individuals with Diabetes , Age 40-75 years, LDL-C 70 to 189 mg/dL
  - moderate-intensity statin therapy
  - estimated 10-year ASCVD risk >7.5%--> high-intensity statin therapy
- Primary Prevention in Individuals without Diabetes and with LDL-C 70 to 189 mg/dL, and estimated 10-year ASCVD risk >7.5% (no DM+70-189,7.5%)
  - moderate- or high-intensity statin therapy

- ASCVD— high intensity
- LDL-C ≥190 mg/dL -- high intensity
- LDL-C 75-189 -- > DM moderate intensity

  DM + 7.5 % high intensity

  -- > no DM +7.5 % mod-high

High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

4. Statin Safety Recommendations -1

- Selection of the appropriate statin and dose in men and nonpregnant /nonnursing women (patient characteristics, level of ASCVD* risk, and potential for adverse effects)
- Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
  - Multiple or serious comorbidities, including impaired renal or hepatic function.
  - History of previous statin intolerance or muscle disorders.
  - Unexplained ALT elevations >3 times ULN.
  - Patient characteristics or concomitant use of drugs affecting statin metabolism.
  - >75 years of age.
  - History of hemorrhagic stroke.
  - Asian ancestry

4. Statin Safety Recommendations -2

- CK should not be routinely measured in individuals receiving statin therapy
- Baseline measurement of CK (creatine kinase)
- During statin therapy, measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue

4. Statin Safety Recommendations -3

- Baseline measurement of transaminase (alanine transaminase; ALT) levels
- During statin therapy, measure hepatic function if symptoms suggesting hepatotoxicity arise (eg, unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera).

4. Statin Safety Recommendations -4

- Decreasing the statin dose may be considered when 2 consecutive values of LDL-C are <40 mg/dL
- Statins modestly increase the excess risk of type 2 diabetes in individuals with risk factors for diabetes
- Statins are listed as pregnancy category X, and should not be used in women of childbearing potential
- caution in individuals >75 years of age , taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens

4. Nonstatin Safety Recommendations

- Eezetimibe : baseline hepatic transaminases
- Safety of Fibrates
  - Gemfibrozil should not be initiated in patients on statin therapy
  - Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin
- BAS (bile acid sequestrants)should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL

Managing Statin Therapy

- Monitoring Statin Therapy
  - Adherence to medication and lifestyle,
  - Therapeutic response to statin therapy,
  - safety should be regularly assessed.
  - fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter.
  - Other safety measurements should be measured as clinically indicated

Managing Statin Therapy

- Optimizing Statin Therapy
  - The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated.

Managing Statin Therapy

- **Insufficient Response to Statin Therapy**
  - In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy
    - Reinforce medication adherence.
    - Reinforce adherence to intensive lifestyle changes.
    - Exclude secondary causes of hyperlipidemia

Managing Statin Therapy

- Use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy.
  - High-intensity statin therapy : LDL–C reduction of ≥50%
  - Moderate-intensity statin therapy : LDL–C reduction of 30 to <50%
  - LDL–C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

Managing Statin Therapy

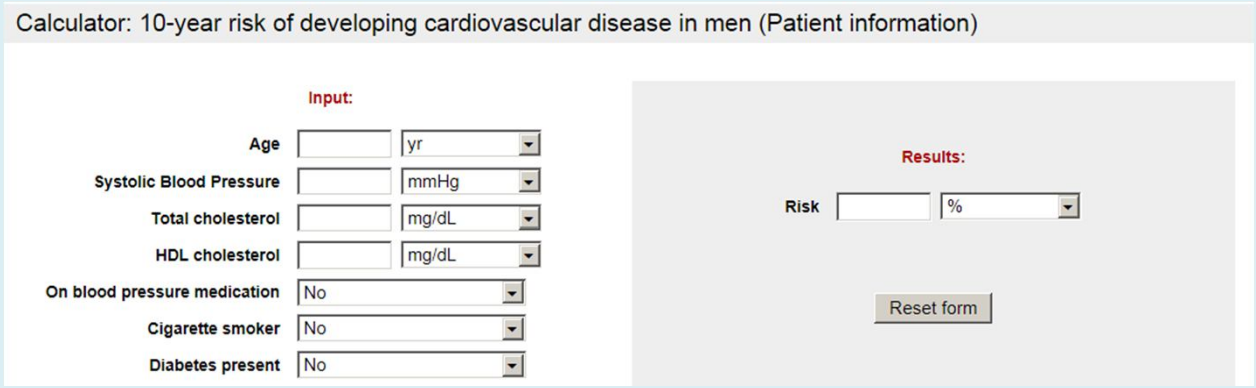
- In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

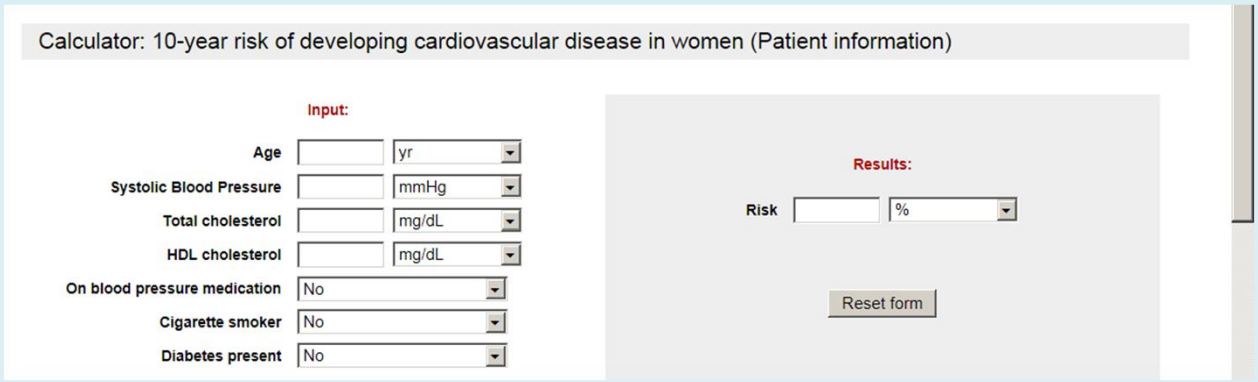
Patient information: High cholesterol and lipids (hyperlipidemia)

- Other risk factors for cardiovascular disease
  - Diabetes mellitus, type 1 and 2
  - Hypertension
  - Kidney disease
  - Cigarette smoking
  - Family history of coronary disease at a young age in a parents or sibling
  - Gender
  - Age
- Lipid types
  - The standard lipid blood tests include a measurement of total cholesterol,LDL, and HDL, and triglycerides.

Patient information: High cholesterol and lipids (hyperlipidemia)

- Calculating risk--Framingham Heart Study





Patient information: High cholesterol and lipids (hyperlipidemia)

- When should i have my cholesterol level tested?
  - Many expert groups have guidelines for cholesterol screening
  - United States Preventive Services Task Force recommends
    - Lipid screening should start at age 35 in men without other risk factors for coronary artery disease and at age 20 to 35 in men with risk factors
    - Lipid screening should definitely start at age 45 and perhaps at age 20 in women with risk factors for coronary disease
- High cholesterol treatments

Case Presentation

Case Presentation 79 y/o female

- Chief Complaint

  Right toes pain for 1 years

- Present Illness

  This 79 year-old female had underlying diseases of

  1.Peripheral arterial occulsive disease, diagnosed in 2015/2

  2.Diabetes mellitus > 20years

  3.Hypertension >20 years

  4.Cataract and glucoma OS s/p operation

  5.Old cerebrovascular accident with facial palsy

- This time she suffered from right toe pain for 1 year. Gangrene change was noted at 2nd toe for >5 months. Numbness was mentioned at left foot. No fever, abdominal pain, chest pain, dysuria, color change or temperature differences at bilateral lower limbs were noted.
- In 2015/2, peripheral vascular test for artery of lower limbs showed severe atherosclerosis of bilateral lower limb's arteries. Under the impression of peripheral arterial occulsive disease with gangrene change at right 2nd toe, she was admitted to our ward for further evaluation and treatment.

- 過去病史:(Past History)

1.Peripheral arterial occulsive disease, diagnosed in 2015/2

2.Diabetes mellitus > 20years

3.Hypertension >20 years

4.Cataract and glucoma OS s/p operation

5.Old cerebrovascular accident with facial palsy

- Personal History :

Allergy:nil

Alcohol (Denied)

Smoking (Denied)

Betelnut (Denied)

- 家族史:(Family History)

no other family members have related diseases

- 理學檢查:(Physical Examination)
  - T:35.9/℃ P:104/min R:16/min BP:132/61/mmHg
  - 體重:52KG (20150524) NRS:0
  - Conscious : Clear
  - HEENT: Sclerae: NOT icteric , Conjunctivae: NOT pale
  - NECK: No jugular vein engorgement
  - CHEST: Breathing sound clear, no wheezing HEART:
  - HEART: S1,S2 normal, Regular heart beat with grade 2 systolic murmur
  - ABDOMEN: Soft AND flat no Murphy`s SIGN
  - EXTREMITIES: Freely movable

	Radial	femoral	dorsalis pedis
Left	++	+-	+-
Right	++	+-	-

Echocardiographic Report

- LVEDD(mm) = 37 LVESD(mm) = 20
- LVEF M-mode(Teichholz) = 78.1 %
- Conclusion:
  1. Adequate LV & RV systolic function with normal wall motion
  2. Thick IVS & mitral annulus calcification
  3. Grade I LV diastolic dysfunction

Laboratory data

Biochemistry

BUN/Cr	10.2/0.63
Na/K	131/4.0
Chol/TG	201/189
HDL/LDL	/138
GPT	12
AC/PC	137/104 (FS)
HA1C	6.7 %

CBC/DC

WBC	6.9 1000/uL
Hb	10.1 g/dL
HCT	29.5 %
Platelet	307 1000/uL
Segment	89.8 %
CRP	73.5 mg/L

U/A

pH	7.5
Protein	2+
Glucose	-
Ketone	-
RBC	3
WBC	27
Epi-	0
Bacteria	+

Urine Culture

E coli	> 100000

Impression

- 1.Peripheral arterial occlusive disease
- 2.Diabetes mellitus
- 3.Hypertensive heart disease
- 4.Neurogenic bladder on Foley catheterization
- 5.Old cerebrovascular disease with facial palsy
- 6.Dyslipidemia
- 7.Normocytic anemia
- 8. Urinary tract infection

Medication

Drugs /date	6/22	6/24	6/25	6/26	6/27
Irbesartan (300)	1 qd				
Amlodipine(5)	1 bid			1 qd	DC
Aspirin	1 qd				
Janumet	1 bid				
Acarbose	1 tid				
Insulin glargine	16U hs				
Theophylline	1 qd				
Farmotidine (20)	1 bid				
Cilostazol (50)	1 bid				
Atorvastatin (10)	1 qd				
Carvedilol(25)				½ bid	
Cefadroixil ->Cefuroxime		2 q12h		1 q12h	
Ultracet tab				0.5PC Q6H	

BP /HR 9am	136/63,84	136/63,84	158/77,96	121/61,80	125/79,73
BP /HR 5pm	161/69	140/70	152/78	113/58	125/79
AC/PC FS	137/104	69/147	130/238	146/161	102/161

Medical care in adults with diabetes mellitus

- 79 y/o female
- Evaluation : PAOD, 2nd toe gangrene, Stroke, Neurogenic bladder , CAD ?
- Glycemic control
  - Janumet 1pc bid
  - Acarbose 1pc tid
  - Insulin glargine 16u hs

  - HbA1C :6.7 %,
  - AC/PC :69-146 /104-238 mg/dl

Medical care in adults with diabetes mellitus

- Reducing the risk factor of macrovascular disease
  - Hypertension
    - Lifestyle modification
    - Irbesartan (300) 1pc qd
    - Amlodipine(5) 1pc bid -> qd
    - Carvedilol(25) ½ pc bid
    - BP 125/79 mmHg, HR 73/min
  - Hyperlipidemia
    - Lifestyle modification
    - Drug selectin:Atorvastatin (10) 1pc qd (moderate intensity)
    - Safety : baseline ALT 12 u/L, Cr 0.63 mg/dl

Thanks for your attention