Study, Design and Rationale of Non-communicable Diseases in Nepal (NCD Nepal) Study: A Community-based Prospective Epidemiological and Implementation Study in Rural Nepal

Supplemental material

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Hypertension Protocol

BP ≥140/90:
- Change to alternative agents if on NSAIDs
- SBP 140-149 or DBP 80-89
  - Lifestyle Modification*
  - F/U in 2-4 wks
    - Yes: SBP ≥130 or DBP ≥80 plus either have ASCVD or ASCVD risk ≥10%
    - No: 1-2 year F/U
  - Yes: BP ≥140 or ≥90
    - Lifestyle Modification*
    - Check labs if known clinician diagnosed HTN
    - BP lowering meds + labs (serum creatinine, lipid profile, urine dipstick; offer TSH and EKG if possible)
      - Yes: BP <130/80
        - No: F/U in 2-4 wks
      - F/U in 3-6 months
        - Yes: Continue current Rx. Confirm adherence* F/U in 6-12 mo with yearly K* & creatinine
        - No: Assess lifestyle & meds adherence*
          - BP <130/80
            - Yes: F/U in 3-6 months
            - No: Consult NCD team if BP uncontrolled
  - Yes: Check K*, & creatinine in 2-4 wks if Lisinopril, Losartan or thiazide started. Check Na in a 2-4 wks in ≥65 yrs if thiazide started.
    - If ≥1+ albumin on dipstick, check urine albumin/Cr
      - Yes: Recheck urine albumin/Cr after 1 year Rx with ACEi/ARB
      - No: Consider increasing dose or adding another first-line drug if adherence* confirmed (Amlodipine+Lisinopril/Losartan combo preferred if feasible)

*Check K only if on ACEi/ARB/thiazides
Monitor K & creatinine yearly only if on ACEi/ARB/thiazides
*Reassess adherence to lifestyle modification & medication on each f/u. Use show card to counsel.
Supplemental figure 1. Hypertension protocol

- Measure BP following BP measurement checklist. Goal BP is <130/80 (i.e. both SBP <130, DBP <80) for most people.
- Measure 3 BP for all participants and take average of last 2 BP measurements. This average BP should be used in the algorithm for treatment decisions.
- Specific antihypertensive medication can vary as long as it belongs to same antihypertensive class (e.g., enalapril instead of lisinopril).
- Angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) is preferred in people with CKD or albuminuria, including people ≥65 years. Without these, amlodipine (or similar calcium channel blocker, CCB) is preferred in people ≥65 years.
- If the preferred antihypertensive medication is not available but non-preferred (e.g., beta blockers) is available, start the latter over none.
- If sodium level in a few weeks after initiating thiazide diuretics in ≥65 yrs is <130 mEq/L, consider switching to an alternative medication. If thiazide is continued, further repeat sodium is needed only if symptom presumed to be from hyponatremia is present. If sodium is 130-135 mEq/L, continue thiazide diuretics without repeat sodium.
- If on amlodipine (or other CCB), checking creatinine at 1 yr f/u is not necessary.
- If creatinine increases by >30% after starting ACEi/ARB or thiazide diuretics, consider using alternative medication.
- Consider using alternative medication, if potassium >5 mEq/L after initiating ACEi/ARB.
If F ≥ 126 or R ≥ 200 or HbA1C ≥ 6.5%, check creatinine, lipid profile, urine dipstick

Urine albumin/Cr

≥1+ urine albumin

Capillary glucose level

F < 100 or R < 140

2 year F/U

F ≥100 or R ≥140

Known clinician diagnosed diabetes

Lifestyle modification*

Check HbA1c

F 100-125 or R 140-199 & HbA1C ≤ 6.4%

Lifestyle modification* & repeat capillary glucose & HbA1C in 1 year

Begin pharmacotherapy for following groups#

Group 1

6.5% ≥ HbA1C < 9%

Group 2

F ≥ 126 or R ≥ 200 & polydipsia + polyuria

Clinic F/U, repeat glucose & HbA1C in 6 mo; Cr in 1 year

Group 3

HbA1C ≥ 9%

Clinic F/U & repeat glucose in 3 months

F/U for Group 3

F ≥ 130 or R ≥ 180

Consider 1st adding SGLT2i, other oral agents injectables & then insulin. Consult NCD team

*Principle of metformin therapy

1. Exclude pregnancy
2. Start metformin 500 mg BID (only if eGFR > 45) for all groups; up titrate to 1000 mg BID in few weeks, esp. for group 3
3. Consider statin therapy, see hyperlipidemia protocol
4. If albuminuria > 300 mg/g or BP > 130 or > 80, add Lisinopril 5 mg or Losartan 25 mg daily then titrate dose.
5. Check K in 2-4 wks if on ACEi/ARB
6. Encourage home glucose monitoring

Recheck urine albumin/Cr every year in all people with diabetes

Fasting means no calories for 8 hours

*Lifestyle modification includes

150 mins of moderate intensity aerobic exercise per week (or 30-60 mins/day)
Encourage diet high in fruits, vegetables, nuts, whole grains, beans, seeds, olive oil, fish, low fat dairy
5-10% body weight loss
Smoking cessation
Supplemental figure 2. Type 2 diabetes mellitus protocol

- Capillary glucose is fasting (F) or random (R) glucose.

- In individuals with F≥126 mg/dL or R≥200 mg/dL, begin pharmacotherapy after confirming hemoglobin A1C (HbA1C) ≥6.5%. Begin pharmacotherapy also when F≥126 mg/dL or R≥200 mg/dL and has both polydipsia + polyuria, and check HbA1C. All individuals with elevated glucose levels (i.e., F≥100 mg/dL or R≥140 mg/dL) but HbA1C <6.5% are managed with lifestyle changes and followed up in a year with repeat HbA1C.

  - Although achieving specific HbA1c goals are not associated with improvement in all diabetes complications, for practical reasons, reasonable HbA1c goals include:
    - 6.5% if newly diagnosed diabetes, diabetes of short duration (~3 yrs), expected long life expectancy and no significant cardiovascular disease
    - <7.5% (or 90 -130 FBG) in healthy older adults ≥65 years
    - <8.5% (or FBG 100-180 mg/dL) in patients with end-stage chronic illnesses

- HbA1c may not be reliable in hemolytic anemia, recent blood transfusion, end-stage renal disease and pregnancy. In such a scenario, fasting blood glucose should be relied upon.

- For most non-pregnant individuals with diabetes, recommended preprandial glucose level is 80-130 mg/dL and peak postprandial glucose level is <180 mg/dL.

- All patients treated with diabetes should be educated about signs and symptoms of hypoglycemia.
• If feasible, it is reasonable to check HbA1C every 3-6 months after initiating or changing pharmacotherapy. Check serum creatinine annually after starting metformin. If estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m², switch metformin to alternate medication.
• Metformin should be cautiously used in liver diseases and congestive heart failure. It is contraindicated if eGFR <30 mL/min per 1.73 m², and should be stopped before surgery or iodinated contrast exposure. Ideally, either screen or treat with vitamin B 12 if on metformin for several years.
• There is no role of ACEi or ARB in diabetics if both BP and urine albumin creatinine ratio is normal. If one of them is abnormal, ACEi/ARB use is justified.
• For patients with diabetes refer for PPSV23 (23-valent pneumococcal polysaccharide vaccine), annual influenza, 3-dose series of hepatitis B, if possible.
• The type 2 diabetes protocol does not apply to management of type I diabetes, management of which is primarily insulin based. However, monitoring framework, including surveillance for diabetes complications are similar as for type 2 DM.
• In people with diabetes, presence of chronic kidney disease or albuminuria further increases the risk of atherosclerotic cardiovascular disease.
• Try checking urine albumin to creatinine ratio on the first-morning sample. Exercise within 24 hrs, infection, fever, congestive heart failure and menstruation can give falsely high albumin in urine.
• Consider adding insulin if initial blood glucose is >300 mg/dL or HbA1C >10% and patient has persistent uncontrolled hyperglycemia, especially after using at least 2 other oral agent (preferably sodium-glucose co-transporter 2 inhibitor) and other injectable agent (eg. glucagon like peptide 1 agonists) – in other words, insulin is the last preferred agent. Similarly sulfonylurea is also not the preferred agent.

• Refer all patients with diabetes for yearly dilated eye and dental exam, if feasible.

• Perform comprehensive foot exam in all patients with diabetes: look for skin integrity especially between toes and under metatarsal heads. Also look for callous, ulcer, foot pulse, loss of protective sensation (monofilament and vibration). Suggest avoiding barefoot outside the house and periodic self-inspection for ulcers. Refer for further testing such as ankle brachial index, as indicated.
**Hyperlipidemia Protocol**

1. **Clinical ASCVD**
   - Yes → Check lipid profile in 3 months of Rx
   - No → High intensity or max tolerated statin

2. **Non-HDL-C ≥220 mg/dL**
   - Yes → Goal non-HDL-C <130
   - No → Consult NCD team if non-HDL ≥130 mg/dL after max tolerated statin

3. **Non-HDL-C 100-219 mg/dL**
   - Yes → If non-HDL-C <100 mg/dL & no DM, F/U in 2 yr with lipid profile
   - No → Check lipid profile in 3 months of Rx

4. **Diabetes mellitus**
   - Yes → Moderate intensity statin
   - No → Consult referral to NCD cardiologist if non-HDL-C >190 or TG>400

*Calculate 10 year ASCVD risk*

*Risk modifiers includes presence of CKD or family h/o premature CAD. Start moderate intensity statin if risk modifiers present in this group, otherwise F/U in 2 years.*

- ≥7.5% to <20%, intermediate risk → High intensity or maximally tolerated statin
- ≥20%, high risk → F/U in 2 year with lipid profile
- 5 to <7.5%, borderline risk* → F/U in 2 year with lipid profile
- <5%, low risk → F/U in 2 year with lipid profile

*Consider referral to NCD cardiologist if non-HDL-C >190 or TG>400*
Supplemental figure 3. Hyperlipidemia protocol

- After lifestyle modification, statin therapy is the cornerstone of pharmacotherapy of hyperlipidemia.
- Note that groups 1 to 4 are in hierarchical order. This means every patient should be assessed if they belong to group 1, then group 2, then 3 and finally 4 in this order. A patient fulfilling requirements of any 2 groups, by definition belongs to the upper hierarchy.
- High intensity statin (typically lowers low-density lipoprotein cholesterol [LDL-C] by ≥50%): Atorvastatin 40-80 mg daily, Rosuvastatin 20-40 mg daily, Simvastatin 80 mg daily (least preferred among the 3 high intensity statins, due to higher propensity for side effects).
- Moderate intensity statin (typically lowers LDL-C by 30-49%): Atorvastatin 10-20 mg daily, Rosuvastatin 5-10 mg daily, Simvastatin 20-40 mg daily.
- Low intensity statin (typically lowers LDL-C by <30%): Rest of the statin dose combinations other than above.
- Consider starting moderate to high intensity statin dose as recommended in the protocol. If the patient can’t tolerate the recommended dose, use the maximally tolerated dose. Consult NCD team if intolerant to 2 different statins.
- Every doubling of statin dose is presumed to have incremental 6% LDL-C reduction.
- Contraindication to aspirin includes active bleeding or recent bleeding (in gastrointestinal and genitourinary tracts, or intracranial bleeding) in the past 6 months, as per discretion of the local provider.
• For those with first group (known AtheroSclerotic CardioVascular Disease, ASCVD) or second group (non-high-density lipoprotein cholesterol ≥220 mg/dL), statin can be started after ≥21 years.

• ASCVD risk refers to atherosclerotic cardiovascular risk and estimates 10-year risk for stroke and heart attack using variables such as age, sex, total and high-density lipoprotein cholesterol, diabetes, systolic blood pressure or their treatment. ASCVD risk score can be calculated using an offline calculator (http://www.cvriskcalculator.com).

• Eventual goal of lipid treatment is to reduce ASCVD. However, a surrogate non-HDL-C goal is <130 mg/dL for all person. For people with multiple ASCVD events or with an established ASCVD and presence of >1 other risk factors, surrogate non-HDL-C goal of <100 mg/dL is reasonable.

• The purpose of repeat lipid profile at 3 months and 1 year after treatment is to confirm adherence to medications and to check response to treatment.

• Non-HDL-C portrays a more complete atherogenic cholesterol than LDL-C and thus preferred.

• Normally non-HDL-C is 30 mg/dL higher than LDL-C, but the difference is higher if triglyceride level is elevated.

• Premature family history of coronary artery disease (CAD) is present if male first degree relative (father/brother/son) had CAD at ≤55 years age or female first degree relative (mother/sister/daughter) had CAD at ≤65 years age. CAD also includes sudden unexplained death.
• All first degree relatives of a person with non-HDL-C ≥220 mg/dL (i.e. presence of familial hypercholesterolemia, FH) should have lipid profile checked because on average 50% of first degree relative will have FH because of predominantly autosomal dominant inheritance pattern of FH-related gene and we have effective treatment available.

• Sometimes people with FH have slightly lower cholesterol. Hence the rationale to refer people with non-HDL-C >190 mg/dL to NCD team.

• The primary treatment approach in people with elevated triglyceride (TG) is lifestyle modification (reduction in carbohydrate and fat intake, alcohol abstinence or reduction and increase in aerobic exercise), which is usually adequate to reduce TG to <150 mg/dL.

• In people with TG >400 mg/dL, first focus on reduction in TG to reduce risk of pancreatitis. After TG is <400 mg/dL, then focus on cholesterol management.

• If TG >400 mg/dL despite intense lifestyle modification (and after confirming adherence to lifestyle change), preferred pharmacotherapy option is icosapent ethyl (2 g twice daily), if available. The second preferred agent is medication from fibrate group (fenofibrate preferred) and the last preferred agent is high dose niacin.

• Consider consulting cardiologist, endocrinologist or NCD team if TG >400 mg/dL despite intense lifestyle modification prior to starting pharmacotherapy.

• Main goal of TG treatment is reducing risk of pancreatitis and perhaps ASCVD. Surrogate goal is to achieve TG <150 mg/dL.
**Tobacco Cessation Protocol**

"Have you used any forms of tobacco in the past 30 days?"

"Have you attempted quitting in the past?"
- **Yes**
  - Explore factors, situations that triggered relapse; use them as learning points. Emphasize multiple attempts is common for successful quitting
  - F/U in-person or via phone in 1 wk, then every 1 mo x 3 mo, then in 1 yr. F/U sooner if barriers encountered.
- **No**

"Are you ready to quit?"
- **Contemplating**
  - Offer motivational interviewing (Help patient identify negative consequences of smoking, potential health and economic benefits of quitting – discuss barriers to quitting such as withdrawal symptoms, psychiatric conditions and social circumstances)
  - Willing to quit?
    - **Yes**
      - Successful in quitting
    - **No**
      - Ask to F/U when determined to quit

**Strategies to deal with craving**
1. 10 deep breaths to relax
2. Drink water to flush out toxins
3. Distract by reading, watching TV, listening to music etc.
4. Avoid other smokers
5. Exercise

**Overcoming barriers to quitting**
1. Identify triggers to smoke: morning tea, alcohol. Develop coping skills (avoid, change or escape high-risk situations)
2. Smoker in the household - ask to bring them on f/u visit for counseling
3. Nicotine withdrawal symptoms – timeline
   - i. Weight gain - try healthy diet and exercise
   - ii. Anxiety/insomnia/irritability - positive self-talk ("This will get easier"), yoga, meditation
   - iii. Follow role models - model their actions/behaviors
   - iv. Seek social support, learn from each unsuccessful attempt

"Congratulations on your journey towards quitting!"
Supplemental figure 4. Tobacco cessation protocol

- All forms of tobacco users (smoke or smokeless, including hukka, tamakhu etc) should receive same counseling about cessation.
- Pharmacotherapy is recommended in any forms of tobacco use
- Choice of pharmacotherapy depends on practical reasons like availability, cost, relapse on prior use etc.
- If someone fails one pharmacotherapy, try another one.
- Ideally, nicotine gum is not used in isolation; it is an adjunct used in combination with other pharmacotherapy

Possible pharmacotherapy for tobacco use

- Nicotine Patch:
  
  >40 cigarettes per day (CPD): 42 mg/day,
  
  ≥21-39 CPD: 28-35 mg/day,
  
  10-20 CPD: 14-21 mg/day,
  
  <10 CPD: 14 mg/day.

- Nicotine gum: >20 CPD: 4 mg, <20 CPD: 2 mg.

- Varenicline: Days 1-3: 0.5 mg/day then 0.5 mg twice/day for 4 days then on target quit date stop smoking and take 1 mg twice/day for 11 weeks.
• Bupropion: 150 mg/day for 3 days, then 150 mg twice/day for 4 days then on target quit date stop smoking. Continue at 150 mg twice/day for 12 weeks