# Managing Multimorbidity Conditions

## 1 TIA/Duodenal ulcer/Osteoporosis (Peleg, Tu)

Alexandra Kogan3, Mor Peleg3, Samson W. Tu4, Raviv Allon1, Natanel Khaitov1, Irit Hochberg1,2

1Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

2Institute of Endocrinology, Diabetes and Metabolism, Rambam Medical Center, Haifa, Israel

3Department of Information Systems, University of Haifa, Haifa, Israel, 3498838

4Center for BioMedical Informatics Research, Stanford University, Stanford, CA, 94305, USA

For patients with history of TIA, secondary stroke prevention is indicated. The recommended medications include aspirin or aspirin+dipyridamole (Class I; Level of Evidence B), or Clopidogrel (Class IIa; Level of Evidence B)[[1]](#footnote-1).

A known side effect of aspirin and other NSAIDs is gastrointestinal bleeding. For long-term prevention of recurrent bleeding ulcers2, the recommendation for patients with low-dose aspirin-associated bleeding ulcers given for secondary prevention of CVD is that “aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1 – 3 days and certainly within 7 days. Long-term daily PPI therapy [proton-pump inhibitor, e.g., omeprazole]\* should also be provided.[[2]](#footnote-2) {Note that PPI has a physiological effect of inhibition gastric acid secretion}.

Post-menopausal patients should be evaluated for osteoporosis.[[3]](#footnote-3) This is done using Fracture Risk Assessment Tool (FRAX) and bone mineral density assessment via axial dual-energy X-ray absorptiometry. When osteoporosis is established, the patient should be evaluated for causes of secondary osteoporosis3. Laboratory evaluation should include a complete blood count (CBC); comprehensive metabolic panel; Serum 25-hydroxyvitamin D, intact parathyroid hormone (PTH); phosphate; and a 24-hour urine collection for calcium, sodium, and creatinine. If the patient is receiving thyroid hormone or there is a suspicion for hyperthyroidism, thyroid-stimulating hormone should also be measured. If there is clinical or biochemical evidence of malabsorption, celiac antibodies should be obtained. Serum and urine protein electrophoresis could be obtained if there is a suspicion for multiple myeloma (e.g., non-PTH mediated hypercalcemia).

If the patient is taking a drug (e.g., PPI) known to be a contributing factor to osteoporosis, consider stopping that drug.

Patients with high risk for future fractures (>=20%) should be given medications to reduce the risk: alendronate, risedronate, zoledronic acid, or denosumab3.

**Patient case:** Mrs. Williams is a 76 year old female, height 172cm, weight 70kg, BMI: 23.7

Current problems: TIA, DU

**Current medications**: Aspirin, Nexium (PPI) The patient is on aspirin for secondary prevention of stroke (due to her TIA 13 years ago) and on PPI to protect the duodenum and prevent ulcer bleeding, because she had duodenal ulcer 4 years ago, due to aspirin.

**New problem**: Osteoporosis

**Management scenario**: The patient presented recently with back pain. Earlier lumbosacral X-ray showed no vertebral fracture and the physician decided to follow primary care recommendations to evaluate risk for osteoporosis fractures, and thus ordered a DXA bone mineral density scan. Osteoporosis was confirmed (DXA shows bone marrow density of -2.6. FRAX assessed and risk of second fracture is >20%). The recommended blood tests were ordered to rule out additional reasons for secondary osteoporosis.

Osteoporosis was diagnosed and all blood tests were normal (including electrolytes, vitamin D, thyroid function, protein electrophoresis, CBC, and metabolic panel). In addition, the patient does not have conditions that may be a secondary cause such as Diabetes or Celiac or a family history of them. A possible secondary cause of osteoporosis is Nexium (PPI).

**Adverse interactions and revisions:** Based on the three guidelines, there are 3 options:

Option 1: (all goals met).

* switching aspirin to clopidogrel (antiplatelet that is not an NSAID - for secondary prevention of stroke),
* stopping PPI (to decrease osteoporosis), PPI no longer needed to prevent DU because aspirin was stopped
* adding alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk of fracture.

Option 2: (Secondary Osteoporosis prevention goal unmet. Only Osteoporosis treatment is met).

* keeping aspirin (antiplatelet for secondary prevention of stroke)
* adding PPI long-term (secondary prevention of DU),
* adding alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk of fracture.

Option 3: (DU protection goal unmet)

* keeping aspirin (antiplatelet for secondary prevention of stroke),
* stopping PPI (to prevent worsening of osteoporosis),
* adding alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk of fracture.

## 2 Chronic kidney disease/hypertension/atrial fibrillation

Wojtek Michalowski1, Szymon Wilk2, Martin Michalowski3, Marc Carrier4, Gregoire Le Gal4, Stephen Kingwell5

1Telfer School of Management, University of Ottawa, Ottawa, ON, Canada

2Institute of Computing Science, Poznan University of Technology, Poznan, Poland

3School of Nursing, University of Minnesota, Minneapolis, MN, USA

4Division of Hematology, The Ottawa Hospital, Ottawa, ON, Canada

5Division of Orthopaedic Surgery, The Ottawa Hospital, Ottawa, ON, Canada

Management of the chronic kidney disease (CKD) depends on the stage of the disease and is determined by checking the estimated glomerular filtration rate (eGFR) level[[4]](#footnote-4). A patient with advanced CKD (eGFR < 60) needs to be checked for anemia and if it is present – managed accordingly. Anemic patient with hemoglobin level below 100 g/L should be given erythropoiesis-stimulating agent (ESA, e.g. epoetin alfa or darbepoetin alfa). Moreover, if the patient’s ferritin level is below 100 ng/mL, oral iron therapy is initiated. A patient diagnosed with a metabolic abnormality is prescribed one of the calcium-based phosphate binders (e.g. calcium acetate) to treat high blood phosphorus levels.

Management of hypertension (HTN) should be determined after prolonged period of serial blood pressure (BP) measurements both in a clinic and at patient’s home[[5]](#footnote-5). While there is ongoing discussion regarding what constitutes high BP and the definition often is guideline specific, there is an agreement that people with BP greater than 140/90 mmHg should be considered as candidates for pharmacological HTN treatment combined with lifestyle changes. HTN is treated in three steps, depending if BP is controlled. In step 1, patients who are younger than 55 years are prescribed ACE inhibitor (such as capoten or monopril) while older patients are prescribed calcium channel blocker (CCB) (such as amlodipine or diltiazem). Associated lifestyle changes involve diet (reduction in coffee and alcohol intake, low sodium diet) and exercise. Step 2 treatment, irrespective of patient’s age, involves combining ACE inhibitor with a diuretic (such as chlorthalidone or hydrochlorothiazide). If such treatment does not result in controlled BP, step 3 treatment asks that all patients, irrespective of age, are additionally prescribed CCB medication.

Management of a symptomatic non-valvular atrial fibrillation (AFib) depends on persistence of the symptoms[[6]](#footnote-6). Unless special circumstances are present, rate control therapy is attempted as first line of treatment and it usually involves a beta blocker (BB) or non-dihydropyridine calcium channel blocker (CCB). However, it is suggested that digoxin be considered as a therapeutic option to achieve rate control in patients with AFib and symptoms caused by rapid ventricular rates whose response to BB and/or CCB is inadequate, or where such rate-controlling drugs are contraindicated or not tolerated. Oral anticoagulation therapy (warfarin or DOAC) is always initiated for symptomatic AFib patients to prevent thrombotic event. If rate control does not produce desired results for about 3-4 weeks, rhythm control therapy is initiated and it most often involves dronedarone, flecainide, or amiodarone. Long term maintenance therapy is often combined with the oral anticoagulation.

**Patient case:** John is a 70 years old male managed for CKD and HTN. He has severely decreased kidney function (eGFR = 35, absence of proteinuric CKD), has significant anemia (hemoglobin level of 95), no metabolic disturbances, and stable ferritin level of 110. John’s HTN is managed according to step 3 treatment (capoten (ACE inhibitor), diltiazem (CCB) and chlorthalidone (diuretics)). In addition, John takes low dose aspirin for lowering risk of CVD[[7]](#footnote-7).

**Current problems**: CKD, HTN managed according to step 3 treatment.

**Current medications:** ESA (darbepoetin alfa), Low dose aspirin, ACE inhibitor (capoten), CCB (dilitiazem), Diuretic (chlorthalidone). Dosages for all the medications are optimized at the maximal level for John’s condition. His lifestyle is managed to lower the risk of CVD and control the HTN.

**New problem:** AFib

**Management scenario:** For last year John experienced multiple episodes of irregular heart beat that resolved on its own. However, for last 2 days John is experiencing pronounced irregular heart beat with the increasing intensity of the associated symptoms of breathlessness, dizziness, and chest discomfort. Upon admission to the Emergency Department, John is diagnosed with tachycardia and persistent, highly symptomatic acute, non-valvular AFib that is confirmed by standard ECG recording.

John’s CHA2DS2-VASc score is greater than 2.

As a first line of urgent treatment John is administered intravenous heparin and his condition is stabilized with urgent direct-current cardioversion that results in significant improvement of the symptoms of AFib.

**Adverse interactions and revisions:** AFib is a newly diagnosed condition for John and long-term treatment following the diagnosis impacts his current therapy for CKD and HTN.

1. Considering current episode of AFib, CVD prevention (see the CKD guideline) needs to be more aggressive and low dose aspirin needs to be replaced with anticoagulant such as warfarin[[8]](#footnote-8).
2. Considering that John has persistent and highly symptomatic AFib with symptoms improved after urgent cardioversion, his anti-arrhythmic therapy might include potassium channel blocker (PCB) such as amiodarone. However, amiodarone is contra-indicated for patient diagnosed with CKD and it is advised to prescribe sodium channel blocker (SCB) such as propafenone[[9]](#footnote-9).
3. Considering that John experienced tachycardia, he should be prescribed BB for rate control and also for recurrence prevention in long term AFib pharmacological therapy. However, combining BB medication with ACE inhibitor or with non-dihydropyridine CCB (such as diltiazem) is not recommended, so BB medication should not be prescribed[[10]](#footnote-10).

**John’s preferences:** To have warfarin replaced by one of the DOACs (apixaban) in order to avoid hassle around checking the INR level on a regular basis.

**Revised treatment for CKD, HTN, and AFib:** ESA, DOAC, ACE inhibitor, CCB, Diuretic, SCB (all medications are at their optimal levels for John’s condition).Lifestyle management to lower the risk of CVD and control HTN, as previously. John was advised to report immediately to his physician if experiencing any bleeding.

Considering that John is prescribed ACE inhibitors, his kidney function needs to be tested within the next 3 months for possible deterioration. It is also advised that while conducting the blood test, at the same time the patient has the ECG test to assess efficacy of prescribed treatment for AFib.

## 3 Venous Thromboembolism /Urinary tract infection (Van Woensel, Abidi)

Guidelines for Venous Thromboembolism (VTE) prescribe treatment with DOACs (preferred line of treatment) or warfarin[[11]](#footnote-11). For bacterial urinary tract infection (UTI), guidelines recommend treatment with an antibiotic such as trimethoprim–sulfamethoxazole (TMP/SMX) because of its low cost, effectiveness and familiarity among clinicians. The primary mechanisms by which antibiotic medications interact with warfarin to increase the risk of major bleeding is through disruption of intestinal flora that synthesize vitamin K, and inhibition of cytochrome p450 isozymes which metabolize warfarin. Interactions between warfarin and specific antibiotic agents have been widely assessed[[12]](#footnote-12) [[13]](#footnote-13). The antibiotics most likely to interfere with warfarin are TMP/SMX, ciprofloxacin, levofloxacin, metronidazole, fluconazole, azithromycin, and clarithromycin. Low-risk agents include clindamycin, cephalexin, and penicillin G[[14]](#footnote-14). Notwithstanding, treatment with TMP/SMX is still considered an effective management option for VTE/UTI comorbidity, as long as the risk of bleeding, as indicated by the International Normalized Ratio (INR), is carefully monitored[[15]](#footnote-15). When the risk of bleeding increases, the warfarin dose has to be reduced to compensate; once INR values return to normal, the original warfarin dose should be reinstated.

**Patient case**: Sixty-seven-year-old female on a long-term anticoagulation therapy (warfarin due to financial considerations) because of recurrent VTE.

**Current problem**: Recurrent VTE

**Current medication**: warfarin (5mg/day)

**New problem**: UTI

**Management scenario**: Patient presents with the symptoms of a strong and persistent urge to frequently urinate and describes experiencing burning sensation when urinating. A preliminary diagnosis of the cystitis UTI is confirmed by lab results. Considering that for last episode of the UTI, she was prescribed TMP/SMX (Bactrim, 2 double-strength tablets orally, twice daily for at least 3 days) and it was well-tolerated, similar treatment for current episode of the cystitis UTI was followed[[16]](#footnote-16).

**Adverse interactions and revisions**: Because of the interactions between warfarin and TMP/SMX, a pre-emptive reduction 10% of warfarin dosage is recommended[[17]](#footnote-17). Considering her total weekly warfarin dose is 35 mg, her reduced daily dose becomes 4.5 mg per day (calculated as (35 – 3.5)/7 = 4.5).

Beginning on day 3 of therapy, INRs should be measured daily and warfarin doses adjusted to achieve an INR >= 2.0 as soon after day 3 of overlapping therapy as possible[[18]](#footnote-18).

**Revised treatment for VTE and UTI**: warfarin (4.5mg/day), bactrim (2 regular strength tablets/day for at least 3 days). Re-evaluate starting on day 3 of overlapping therapy depending on the INR value.

## 4 Drug-eluting Stent / lung mass surgery (Peleg, Tu)

Ruth Edry1,2, Alexandra Kogan3, Mor Peleg3, Samson W. Tu4

1Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

2 Acute pain service, Haifa, Rambam Medical Center, Haifa, Israel

3Department of Information Systems, University of Haifa, Haifa, Israel, 3498838

4Center for BioMedical Informatics Research, Stanford University, Stanford, CA, 94305, USA

Cardiac patients who undergo implantation of drug-eluting stent are placed on dual anti-platelet therapy[[19]](#footnote-19): aspirin + P2Y12 inhibitor for 12 months. Note that at this stage, the patient is not at high risk for bleeding. Three P2Y12 inhibitors are indicated: Ticagrelor, Prasugrel, or Clopidogrel.

When a patient with high cardiovascular risk needs to undergo a vital surgical procedure that cannot be postponed till 12 months after the stent implantation, he is also at high risk for surgical bleeding.

According to the guideline on Perioperative Antiplatelet Therapy[[20]](#footnote-20), aspirin should be maintained and clopidogrel needs to be stopped five days before surgery. As explained in this guideline “After cessation of aspirin or clopidogrel, platelet aggregation returns to baseline in five days.” This reduces the risk of bleeding during surgery, due to decreased platelet aggregation.”

Possible bridging therapy (substitution of clopidogrel) three to five days before surgery with intravenous tirofiban (Aggrastat) or eptifibatide (Integrilin) is indicated19,[[21]](#footnote-21). As stated in20, clopidogrel is to be withdrawn 5 days before surgery, and tirofiban started 24 h later, continued until 4 h before surgery, and resumed 2 h after surgery until oral clopidogrel is resumed.

After the operation, antiplatelet therapy is resumed within the first 12 to 24 hours; clopidogrel therapy is reinitiated with a 300-mg loading dose, which reduces the time to achieve maximal platelet inhibition to four to six hours and decreases the risk of hyporesponsiveness from competition of other drugs with hepatic cytochromes19.

**Patient case:** Mr. Grant is a 73 year old male, height 183 cm, weight 80 kg, BMI: 23.9.

**Current medications**: Aspirin, Clopidogrel

**Current problem:** MI and 2 months post Drug-eluting Stent surgery

**New problem:** Lung mass

**Management scenario**: Patient had MI and the doctors decided to implant a drug-eluting stent. Accordingly, the patient was placed on dual anti-platelet therapy: aspirin + clopidogrel for 12 months.

Two months after the stent implantation, the patient was diagnosed with a lung mass and surgery is indicated and cannot be postponed till dual antiplatelet therapy is completed.

1. Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack, 2014, Stroke, p. 2198 [↑](#footnote-ref-1)
2. Management of Patients with Ulcer Bleeding, 2012, American Journal of Gastroenterology, p. 3. [↑](#footnote-ref-2)
3. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. 2016, Endocrine Practice. pp. 3,6,14,15 [↑](#footnote-ref-3)
4. Guidelines for the Management of Chronic Kidney Disease, 2008, CMAJ. See p. 1154, 1158, 1159, 1160 (highlighted). [Levin-2008] [↑](#footnote-ref-4)
5. Hypertension in adults: diagnosis and management. 2019, NICE Guideline. See p. 5, 9, 12, 14, 15, 16 (highlighted). [NICE-2019] [↑](#footnote-ref-5)
6. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology 2018; 34 (11): Online Supplement. See p.9, 12, 13, 21 (highlighted). [Andrade-2018]. [↑](#footnote-ref-6)
7. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2019, Journal of American College of Cardiology. See p. e204 (highlighted). [Arnett-2019] [↑](#footnote-ref-7)
8. Antiplatelet therapy for stroke prevention in atrial fibrillation. Missouri Medicine2010; 107 (1): 44-7. See p. 45, 46 (highlighted). [Garg-2010] [↑](#footnote-ref-8)
9. Understanding and Managing Atrial Fibrillation in Patients with Kidney Disease. Journal of Atrial Fibrillation2015; 7 (6): 1069. See p. 64 (highlighted). [Khouri-2015] [↑](#footnote-ref-9)
10. Combining other antihypertensive drugs with beta-blockers in hypertension: a focus on safety and tolerability. Canadian Journal of Cardiology2014; 30 (5 Suppl): S42-6. See p. s43, s44 (highlighted). [Richards-2014] [↑](#footnote-ref-10)
11. Wells, G. et al. Directoral Anticoagulants For The Treatment Of Venous Thromboembolic Events.   
    <https://www.ottawaheart.ca/sites/default/files/uploads/documents/Researchers/gwells-doac-vte-scientific-report-2015-2016.pdf> (cannot find a journal reference) (p. 8, highlighted) [↑](#footnote-ref-11)
12. Fischer HD, Juurlink DN, Mamdani M, Kopp A, Laupacis A. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents. Archives of Internal Medicine. 2010;170:617–21. [↑](#footnote-ref-12)
13. Glasheen JJ, Fugit RV. How warfarin interacts with common antibiotics. Emergency Medicine. 2004;36:30C–I. [↑](#footnote-ref-13)
14. Onysko M, Holcomb N, Hornecker J. Antibiotic interactions: Answers to 4 common questions. The Journal of Family Practice. 2016; 65(7): 442-448. [↑](#footnote-ref-14)
15. See “Practical management with Warfarin”, p. 1, p. 5 (highlighted). [↑](#footnote-ref-15)
16. See “International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women” (p. 3, highlighted) [↑](#footnote-ref-16)
17. Ahmed A, Stephens JC, Kaus CA, et al. Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin. Journal of Thrombosis and Thrombolysis. 2008;26:44-48. [↑](#footnote-ref-17)
18. See “Practical management with Warfarin”, p. 1, p. 5 (highlighted). [↑](#footnote-ref-18)
19. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. European Heart Journal (2018) 39, 213–254; doi:10.1093/eurheartj/ehx419, p. 233 first row of table and Figure 4 – green box on the right [↑](#footnote-ref-19)
20. Perioperative Antiplatelet Therapy (2010). P G Chassot, C Marcucci, A delabays, D R Spahn, SPAHN. Am Fam Physician. 2010 Dec 15;82(12):1484-1489. Table 3 bottom right. [↑](#footnote-ref-20)
21. Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of ‘bridging’ antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. S. Savonitto, M. D’Urbano, M. Caracciolo, F. Barlocco, G. Mariani, M. Nichelatti, S. Klugmann and S. De Servi. British Journal of Anaesthesia 104 (3): 285–91 (2010). doi:10.1093/bja/aep373, last paragraph. [↑](#footnote-ref-21)