(MATE) Metformin and Aging Trial in the Elderly: A Pilot and Feasibility Study

NCT03451006

10/5/2020

(MATE) Metformin and Aging Trial in the Elderly: A Pilot and Feasibility Study

Abstract. Metformin exerts its effect on health span as a calorie restriction-mimetic through activation of AMP-activated protein kinase. This drug is safe, inhibits cellular senescence, and prolongs life in mammals. We hypothesize that chronic metformin administration through augmentation of cellular regeneration and inhibition of senescence improves physical functioning of older adults. In this pilot, feasibility study, we aim to administer metformin up to 2 gm or placebo in a 1:1 randomized fashion for one year to 12 frail adults, ≥ 60 years with coronary artery disease and assess their physical function by frailty measures . Among patients with improved physical function throughput profiling of tissue and serological samples will be made to establish a molecular map of the impact of metformin. The effect of metformin on several senescent markers (IL-6, MCP-1, MMP-3/9/12, PAI-1/2, and activin A) will be tested as well.

Version: 4

Date: October 5, 2020

Principal Investigator: Mandeep Singh, MD, MPH

A. Rationale: Heart disease is the number one cause of death in the United States and disproportionately affects older adults, underscoring the need to examine determinants of survivorship.[1-3] Recognizing this gap, ACC/AHA guidelines lay emphasis to assess frailty, a key construct prevalent in elderly and known to impact their prognosis.[1, 2, 4, 5] Older persons are commonly frail, and their health span is truncated by illnesses during which physiological declines together with accumulation of additional deficits results in multimorbidity and functional dependence.[6-8] High incidence of functional decline in patients with coronary artery disease (CAD) [9, 10] makes pharmacologic manipulation, an attractive strategy to improve frailty and reduce adverse cardiovascular outcomes. Metformin exerts its effect on health span as a calorie restriction-mimetic through inhibition of mitochondrial complex 1 and activation of AMP-activated protein kinase.[14] This drug is safe and has been shown to prolong life in mammals.[15] Metformin by reducing effects of cellular senescence may improve the functioning of older adults.

In CAD, cellular senescence and inflammation affect organ dysfunction through interference with tissue homeostasis and regeneration.[16-18] The deleterious effect of senescence includes pro-inflammatory senescence-associated secretory phenotype (SASP).[19] Normal biological function through alteration in cellular homeostasis may be achieved by metformin. The phenotypic manifestations of these changes are incompletely characterized as it is yet unknown whether cell-intrinsic regenerative mechanisms can be translated into clinical improvement in physical performance and whether it's chronic administration is safe in older adults. These major gaps in knowledge hinder utilization of metformin as an agent to promote cellular regeneration and to reduce the impact of cellular senescence.

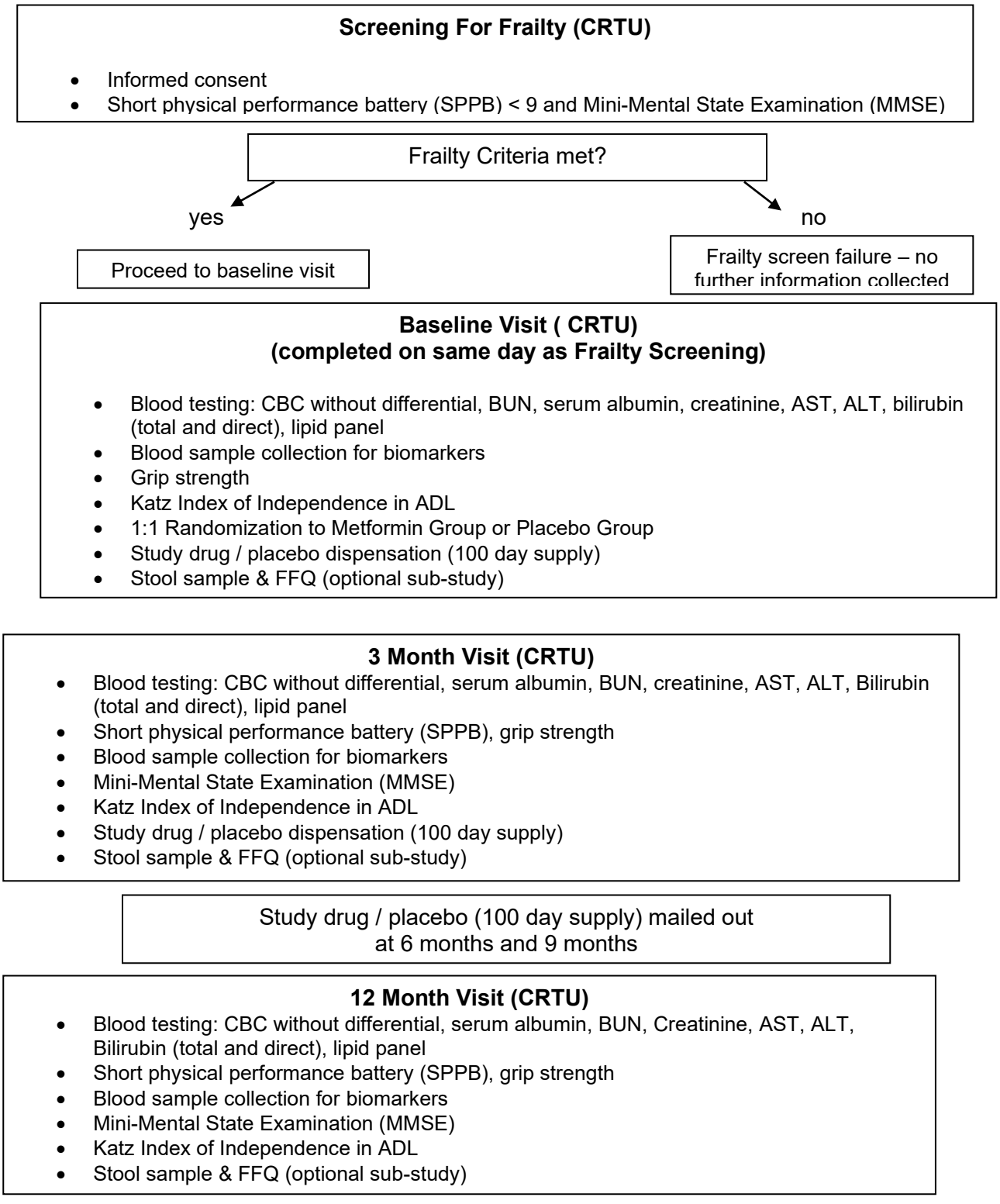
Targeting frail individuals with high levels of inflammation and SASP factors would necessitate identification of predictors of improvement with metformin in tissue inflammation and function. A clinomics approach implementing simultaneous assessment of clinical impact coupled with OMICs-based serological profiling would provide enhanced understanding of the local and systemic impact mediated by metformin. Through correlation of molecular profiles with phenotypic expression changes, as proposed herein, we will enhance our understanding of the regenerative impact of metformin and the basis for clinical improvement in the setting of senescence.

B. Hypothesis: Chronic metformin administration through augmentation of cellular regeneration and reduction of senescence will improve frailty and physical functioning.
C. Innovation: This would be first-in-human pilot safety and feasibility study. There are no studies that have investigated the anti-aging potential of metformin.

D. Significance: 1. If proven, metformin will be given to improve physical functioning patients with CAD. Larger phase 3 studies would be needed. 2. This will enhance the reputation of Mayo Clinic, attract unique patients, and advance our knowledge about cardiovascular disease. 3. Increase in AMPK activity by metformin mimics calorie restriction by upregulating macroautophagy, mitochondrial biogenesis, inhibiting mTOR-1 allows cells to be functionally fit.[14, 20, 21] TOR complex 1 can be successfully inhibited by metformin to slow senescence and improve human health.[21] Metformin also inhibits cellular senescence, a key mammalian longevity pathway.[22-24] Metformin extends lifespan in nematodes and mammals.[25-27] It is safe and prevents progression from impaired glucose tolerance to clinical diabetes.[28] Metformin among diabetics reduces risk of cardiovascular disease further supporting its role in attenuating age-related chronic diseases.[29-36] Role of metformin as a pharmaceutical intervention to prevent aging is not derived from prospective studies.[37] Cellular senescence arrests cells at risk for malignant transformation[19], however, the harmful effects may

manifest through their proinflammatory SASP.[38] The role of metformin in modifying SASP is less well known, it is known to reduce senescence through prevention of translocation of NF-κB.[23]

E. Brief Synopsis of Methods: 12 frail patients ≥60 years with CAD, will be randomized to metformin (up to 2.0 gm) or placebo for 1-year to note improvement in frailty. Molecular map through high throughput serological profiling and assessment of SASP will be done of responders and nonresponders to metformin. An IND exemption is being requested for the use of metformin.



F. Preliminary data to support feasibility: In a prospective cohort study, patients ≥ 65 years who underwent PCI were assessed for frailty (Fried criteria), comorbidity (Charlson index), and quality of life [SF-36].[7] Of the 628 patients discharged, 78 died. Following adjustment, frailty was associated with long-term mortality. In a recent pilot study[39], oral rapamycin (0.5, 1, 2.0 mg) was given for 12 weeks to 13 non-frail patients who underwent PCI. Plasma and adipose tissue markers of senescence were favorably modified by rapamycin [plasma IL-6 decreased from 4.4 to 2.6 pg/ml; adipose tissue mRNA expression of p16 (129 vs. 169), and senescence-associated beta galactosidase activity decreased (2.2% vs. 3.6%). Moderate correlation between some senescence markers and physical functioning was also demonstrated.

Safety of metformin in nondiabetics: The safety of metformin in patients without diabetes is well demonstrated in patients with diverse indications. In the Glycometabolic Intervention as Adjunct to Primary Coronary Intervention in ST-segment-elevation Myocardial Infarction (GIPS-III) randomized trial on 380 patients without diabetes mellitus, who received 1 gm of metformin for 4 months, no cases of lactic acidosis were observed.[40] Importantly, the levels of creatinine, glucose, and HBA1C levels did not differ between the groups taking metformin or placebo underscoring the safety of the drug. Higher gastrointestinal side effects, which were self-limiting and did not require discontinuation of metformin were observed in patients with erectile dysfunction who also had insulin resistance as compared to placebo (61.5% vs. 7.7%, P=0.03).[41] Similar results (higher gastrointestinal side effects) were seen with metformin in women with polycystic ovary syndrome (OR 4.49, 95% CI 1.88-10.72)[42] or as an addition to chemotherapy in patients with advanced pancreatic cancer[43] or when given to non-diabetic patients with coronary heart disease (CAMERA study)[44] or with metformin pretreatment in patients undergoing coronary artery bypass surgery.[45]

G. Study design: This will be a pilot, feasibility study. Twelve subjects ≥ 60 years with CAD, who are determined to be frail will be randomized to receive up to 2.0 gm of oral metformin or placebo for 12 months.

Study visits: *Assessments will be done at three predefined time intervals: baseline, 3 months, and at 1 year.* During these visits, workup will include complete blood count, BUN, creatinine, AST, ALT, bilirubin total, bilirubin direct, serum albumin, and fasting lipid panel, frailty assessment with short physical performance battery (SPPB) and grip strength, Mini-Mental State Examination (MMSE), Katz Index of Independence in ADL, stool sample and Food Frequency Questionnaire (optional sub-study), serum markers of senescence and OMICs (see Schedule of Events). All visits will have a +/- two week window for assessment. Measurement of frailty will be done by the study coordinator. A brief self-report regarding recent use of antibiotics, laxatives, and colonoscopy colon prep agents will be done at each visit. At each visit, subjects will be asked about side effects. Subjects with serious side effects from the medications will be withdrawn from the study, Appendix 1.

Recruitment of subjects: Clinics (CAD and Cardiac Education) with high number of patients with CAD will be screened daily for potential participants. We will also screen daily the inpatient census for patients who undergo percutaneous coronary interventions. In addition, we have developed computerized algorithms using inclusion/exclusion criteria (listed below), and diagnostic codes. These algorithms will be applied to the EMR and to the Common Data Model (CDM) established and maintained under IRB 19-005480 (PI: VL Roger, Co-I on this study), to identify potentially eligible subjects. The eligibility also includes absence of known diabetes mellitus and presence of significant renal dysfunction (GFR <45ml/min). If person meets all these criteria (age ≥60 years, absence of diabetes mellitus, and significant chronic renal failure [GFR<45ml/min]), the eligible participants will be contacted via an e-mail/letter. We will send recruitment letters to those who have a high likelihood of being eligible asking if they are interested in participating in the study. If the patient is interested in

participating, we will schedule a phone visit with prescreening questions to determine their likelihood of being frail. If they are deemed likely to be frail, then we will have them come for a screening and baseline visit.

If the patient agrees to participate in the study, the written informed consent will be obtained during the screening and baseline visit before any tests are performed. The consent process will occur in a private setting on the Mayo Clinic campus. The study team member will review the entire consent with the potential participant and answer any questions they may have about the research proposal. The potential participant will be provided as much time as needed to decide whether they want to participate or not. All potential participants will be assured that their clinical care will not be affected in any way if they choose not to participate.

Definitions: Coronary artery disease: Any patient with a diagnosis of CAD will be included. CAD will be defined as patients with history of angina, positive stress test, prior PCI or coronary artery bypass surgery or patients with significant coronary artery disease detected on CT scan. . Patients with known DM or new-onset DM will be excluded. Patients presenting with acute coronary syndrome or patients participating in cardiac rehabilitation will be eligible.

Inclusion Criteria:

- Age ≥ 60 years
- CAD
- Frailty as determined by the short physical performance battery
- Able to return for follow-up
- Written informed consent

Exclusion criteria:

- Pre-existing or new-onset diabetes
- Any active malignancy, hematological disorder, post organ transplant, immunocompromised
- Cancer requiring treatment in the past 3 years (other than non-melanoma skin cancer)
- Dementia [mini mental state examination (MMSE <20)]
- Prior stroke with disability
- Severe Parkinson's
- Hepatic insufficiency and/or chronic liver disease (cirrhosis)
- Chronic kidney disease (GFR < 45 mL/min)
- Taking metformin for any indication
- Acute alcohol intoxication
- Known hypersensitivity to metformin hydrochloride
- Acute/chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma

Measurement of frailty: In prescreening patients via phone, we will ask 6 questions regarding ADLs and self-care to determine who will have a high likelihood of being frail. At the screening visit we will use the short physical performance battery (SPPB; Appendix 2) for identification of eligible participants. We will also measure frailty using the SPPB and grip strength at baseline, 3 months, and at the end of the study. Single-item frailty measures, such as gait speed, grip strength and repeated chair stands (if the participant is able to do), have shown important prognostic value in patients with CAD and will be recorded. Factors that potentially influence frailty (regular exercise regimen, vitamin D supplementation, high protein or calorie-restricted diet, or polypharmacy) will be recorded at each follow-up visit.

Administration of Metformin The gastrointestinal intolerance (diarrhea, nausea, bloating etc.) is associated with higher dose initiation and rapid dose escalation.[47] The pharmacist under the guidance of an endocrinologist will start metformin at a lower dose (500 mg twice a day with meals) and increase the dose at one-week interval to a maximum tolerable daily dose up to 1.0 gm twice a day, depending upon patient's tolerance.[48] Since metformin does not stimulate insulin secretion, hypoglycemia is rarely observed.[49] Randomization to drug or placebo will be done by the statistician to ensure blinding. Administration and monitoring of metformin/placebo will be done by the study coordinator under the supervision of an endocrinologist, who will not be involved in the routine care or follow-up of these patients. The drug will be stopped during hospitalization for repeat angiography, or any acute condition that can adversely affect renal function or can cause lactic acidosis (infection, dehydration etc.). The study medication (placebo or metformin) will be restarted following hospital discharge according to the current FDA recommendations. Renal function will be monitored as a part of their clinical care on follow-up. The drug will be discontinued in patients reporting significant adverse effects.

Plan for alerting the staff for side effects

The most common side effects are gastrointestinal. To reduce the incidence of these side effects, the dose of metformin will be slowly increased and will be given with meals. In the event of intolerable gastrointestinal side effects, the participant will contact the study coordinator via phone call (provided at the time of consent and enrollment). The study coordinator will inform the Principal Investigator and will determine whether a dose reduction is needed (which will be done over the phone) or the participant needs an additional visit. The study coordinator will make a follow-up phone call in one week to inquire whether the side effects have improved/resolved. If they have, the participant will continue with the protocol. If the participant needs to come in due to severity of side effects or the side effects don't resolve, the PI will see the participant and in consultation with the endocrinologist will determine whether to continue the drug, lower the dose, or stop the drug. If the drug is stopped, the final measurements will be done at that time.

Blinding: To ensure blinding, we will take the following steps. The investigators will be blinded to the treatment assignment. The pill count, change in the metformin dose, adverse effect reporting, data entry in the case report form (CRF) will be done by the main study coordinator. Measurement of frailty, MMSE, Katz ADL is done by a second study coordinator who will be unaware of the drug assignment. The pharmacist will not be involved in the routine care or follow-up of these patients. If the discontinuation of study drug is due to serious adverse effects, the principal investigator will contact the primary care provider and further management will be instituted.

Molecular markers: 50 mL of whole blood will be collected for omics assessment. EDTA tubes will be used by the CRTU staff to collect serological samples. The samples will be sent via pneumatic tube shuttle to the Hilton building for pick up by the Behfar study team. Samples will be spun down, processed and/or stored for omics analysis. Study samples will be logged into the RLIMS system for sample management. Five randomly selected serological samples will undergo ELISA-based array evaluation to simultaneously quantify 1200 unique cytokines and growth factors. For non-stochastic evaluation, column-based immunodepletion will be utilized to eliminate albumin from five randomly selected samples prior to 2D-Gel separation and MS spectrometry-based deconvolution to establish the serum proteome. Serum samples will also undergo density filtration followed by rapid lyophilization or density concentration for isolation of the exosomal fraction. Purified serum exosomes will be enriched for small RNAs and subjected to miRNomics analysis. Data sets collected from this cohort will be cross-referenced with clinical frailty following chronic metformin treatment to document regenerative impact at the molecular level. This clinomics-based profiling will provide biomarker

readout to yield a systems-biology map of the mechanistic basis for regenerative benefit in those responsive to metformin therapy. The remaining samples will be stored for future use.

Serum SASP markers: will be measured at baseline, 3 months, and 12 months on all subjects. Serological markers of senescence will include [interlukin-6 (IL-6), matrix metalloproteinase (MMP) 3, 9, and 12, PAI-1 and -2, activin A, and monocyte chemotactic protein (MCP)].

Optional Microbiome Sub- Study protocol: The optional stool samples will be labeled with an ARLIMS tracking number and will be frozen at -80C. At study completion, samples will undergo DNA isolation and subjected to Ribosomal DNA evaluation to delineate and speciate the microbiological content of the stool (Microbiome). For those who agree, a patient stool sample kit will be mailed to each patient prior to their outpatient appointment and will be collected in a fecal tube collection kit prior to their outpatient visit at baseline, 3 month and 12 months. The patient will bring the kit at time of appointment and the sample will be stored in a secured research facility for microbiome analysis. The Mayo Clinic Clinical Research Trials Unit will assist in stool sample pick-up and short-term -80^{o}C storage prior to study staff retrieval.

Food Frequency Questionnaire: An electronic VioFFQ food frequency questionnaire will be administered to those who consent to optional microbiome sub-study, from Viocare Technologies, Inc. to determine dietary patterns over the last 90 days; completed, de-identified questionnaires will be analyzed by a Mayo Clinic research dietician and returned to study staff.

Self-Report: A brief self-report regarding recent use of antibiotics, laxatives, and colonoscopy colon prep agents will be distributed to consenting patients and considered as metadata. These responses may be verified by study staff in a chart review where possible.

Schedule of Events

Tests	Screening Visit	Baseline Visit	3 Month Visit (at conclusion of CR, ± 2 weeks)	12 Month Visit (± 2 weeks)
Informed Consent	X			
Randomization		X		
CBC (without differential)		X	X	X
Serum Albumin		X	X	X
Blood Urea Nitrogen (BUN)		X	X	X
Creatinine (serum)		X	X	X
AST		X	X	X
ALT		X	X	X
Bilirubin (total)		X	X	X
Bilirubin (direct)		X	X	X
Fasting lipid panel		X	X	X
Blood sample collection for molecular & SASP markers		X	X	X
Frailty assessment	X	X	X	X
Mini-Mental State Examination (MMSE)	X		X	X

Katz Index of Independence in ADL		X	X	X
Stool sample (optional sub-study)		X	X	X
Food Frequency Questionnaire (optional sub-study)		X	X	X
Self-report of antibiotics, laxatives, and colonoscopy history		X	X	X

H. Statistical analyses and power considerations: This is a pilot study and will not be powered to detect specific effect sizes. Importantly, measures of variation from this study will be used to power future studies.

I. Human study issues:
Human Subjects Safety: An independent, internal data and safety monitoring board (DSMB) will oversee the progress and safety of the trial and will advise the investigators whether to continue, modify, or terminate the trial. Potential risks to participants may include side effects from metformin. Protection of patient's identity will follow the Department guidelines for handling and storage of research data. Standardized systems to ensure patient confidentiality will be maintained.

Medication safety will be ensured by not giving metformin to anyone who has history of hypersensitivity to metformin or who have moderate-to-severe renal impairment (GFR<45mL/min/1.73m2. Participants on metformin will discontinue the drug to prevent lactic acidosis if they will have a radiologic study with contrast, surgery, excessive alcohol intake, or any other precipitating factors. The only other serious adverse effect of hepatitis will be periodically monitored by blood tests, including serum bilirubin, ALT and AST.

Early withdrawal of Subjects: Participants with serious adverse effects from the medications will discontinue medication use, but will continue with the study visits, unless they wish to completely withdraw from the study. We will make arrangements for the participant to be seen by their primary MD for follow-up. At any other time, patients will contact the main study coordinator, if they develop and want to report any side effects. We will also discontinue medication use if the participants fail to follow the protocol or are unwilling to continue the prescribed medication.
Patients who discontinue the drug will come for their final check-up and will include frailty assessment, and blood draw for biomarkers. We would use intention-to-treat analyses and would not add any other subjects. The subjects who discontinue the study drug will be followed-up by a phone call at one month. If the discontinuation is due to serious adverse effect, the patient will be asked to contact the primary care provider and further management will be instituted.

Stopping Rules: Following rules will be applied to stop the study.
Death of any participant. Following death of any participant, we will stop the study and analyze the cause of death. We will inform IRB and DSMB as well. If the cause of death is unrelated to the drug, then after informing IRB with the permission of DSMB, the study will be restarted. If death is directly related to the drug, the study will be stopped.

In case of nonfatal serious side effects observed in one patient, the drug will be stopped in that patient and trial will be stopped as well.

References

1. Alexander KP, Newby LK, Armstrong PW, Cannon CP, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM and Ohman EM. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation*. 2007;115:2570-89.
2. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM and Ohman EM. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation*. 2007;115:2549-69.
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D and Turner MB. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6-e245.
4. Fried TR and Mor V. Frailty and hospitalization of long-term stay nursing home residents. *J Am Geriatr Soc*. 1997;45:265-9.
5. Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins JA and Gardin JM. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *Jama*. 1998;279:585-92.
6. Singh M, Stewart R and White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J*. 2014;35:1726-31.
7. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS and Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes*. 2011;4:496-502.
8. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED and Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. *J Am Geriatr Soc*. 2006;54:1674-81.
9. Capes SE, Hunt D, Malmberg K and Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773-8.
10. George A, Bhatia RT, Buchanan GL, Whiteside A, Moisey RS, Beer SF, Chattopadhyay S, Sathyapalan T and John J. Impaired Glucose Tolerance or Newly Diagnosed Diabetes Mellitus Diagnosed during Admission Adversely Affects Prognosis after Myocardial Infarction: An Observational Study. *PLoS One*. 2015;10:e0142045.
11. Goel K, Pack QR, Lahr B, Greason KL, Lopez-Jimenez F, Squires RW, Zhang Z and Thomas RJ. Cardiac rehabilitation is associated with reduced long-term mortality in patients undergoing combined heart valve and CABG surgery. *Eur J Prev Cardiol*. 2015;22:159-68.
12. Pack QR, Goel K, Lahr BD, Greason KL, Squires RW, Lopez-Jimenez F, Zhang Z and Thomas RJ. Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery: a community-based study. *Circulation*. 2013;128:590-7.
13. Goel K, Lennon RJ, Tilbury RT, Squires RW and Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation*. 2011;123:2344-52.
14. McCarty MF. AMPK activation--protean potential for boosting healthspan. *Age (Dordr)*. 2014;36:641-63.
15. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M, Pollak M, Zhang Y, Yu Y, Becker KG, Bohr VA, Ingram DK, Sinclair DA, Wolf NS, Spindler SR, Bernier M and de Cabo R. Metformin improves healthspan and lifespan in mice. *Nat Commun*. 2013;4:2192.
16. Ridker PM, Hennekens CH, Buring JE and Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England journal of medicine*. 2000;342:836-43.

17. Matthews C, Gorenne I, Scott S, Figg N, Kirkpatrick P, Ritchie A, Goddard M and Bennett M. Vascular smooth muscle cells undergo telomere-based senescence in human atherosclerosis: effects of telomerase and oxidative stress. *Circ Res*. 2006;99:156-64.
18. Tuomisto K, Jousilahti P, Sundvall J, Pajunen P and Salomaa V. C-reactive protein, interleukin-6 and tumor necrosis factor alpha as predictors of incident coronary and cardiovascular events and total mortality. A population-based, prospective study. *Thromb Haemost*. 2006;95:511-8.
19. Rodier F and Campisi J. Four faces of cellular senescence. *J Cell Biol*. 2011;192:547-56.
20. Hawley SA, Ross FA, Chevtzoff C, Green KA, Evans A, Fogarty S, Towler MC, Brown LJ, Ogunbayo OA, Evans AM and Hardie DG. Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. *Cell Metab*. 2010;11:554-65.
21. Shaw RJ. LKB1 and AMP-activated protein kinase control of mTOR signalling and growth. *Acta Physiol (Oxf)*. 2009;196:65-80.
22. Moiseeva O, Deschenes-Simard X, Pollak M and Ferbeyre G. Metformin, aging and cancer. *Aging (Albany NY)*. 2013;5:330-1.
23. Moiseeva O, Deschenes-Simard X, St-Germain E, Igelmann S, Huot G, Cadar AE, Bourdeau V, Pollak MN and Ferbeyre G. Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-kappaB activation. *Aging Cell*. 2013;12:489-98.
24. Leone A, Di Gennaro E, Bruzzese F, Avallone A and Budillon A. New perspective for an old antidiabetic drug: metformin as anticancer agent. *Cancer Treat Res*. 2014;159:355-76.
25. Anisimov VN, Egormin PA, Piskunova TS, Popovich IG, Tyndyk ML, Yurova MN, Zabezhinski MA, Anikin IV, Karkach AS and Romanyukha AA. Metformin extends life span of HER-2/neu transgenic mice and in combination with melatonin inhibits growth of transplantable tumors in vivo. *Cell Cycle*. 2010;9:188-97.
26. Anisimov VN, Berstein LM, Popovich IG, Zabezhinski MA, Egormin PA, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Kovalenko IG and Poroshina TE. If started early in life, metformin treatment increases life span and postpones tumors in female SHR mice. *Aging (Albany NY)*. 2011;3:148-57.
27. Cabreiro F, Au C, Leung KY, Vergara-Irigaray N, Cocheme HM, Noori T, Weinkove D, Schuster E, Greene ND and Gems D. Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism. *Cell*. 2013;153:228-39.
28. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA and Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine*. 2002;346:393-403.
29. Holman RR, Paul SK, Bethel MA, Matthews DR and Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England journal of medicine*. 2008;359:1577-89.
30. Johnson JA, Simpson SH, Toth EL and Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. *Diabet Med*. 2005;22:497-502.
31. Lamanna C, Monami M, Marchionni N and Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2011;13:221-8.
32. Roumie CL, Hung AM, Greevy RA, Grijalva CG, Liu X, Murff HJ, Elasy TA and Griffin MR. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Annals of internal medicine*. 2012;157:601-10.
33. Whittington HJ, Hall AR, McLaughlin CP, Hausenloy DJ, Yellon DM and Mocanu MM. Chronic metformin associated cardioprotection against infarction: not just a glucose lowering phenomenon. *Cardiovasc Drugs Ther*. 2013;27:5-16.
34. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO and Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care*. 2010;33:322-6.
35. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH and Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer*. 2011;11:20.
36. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD and Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care*. 2009;32:1620-5.
37. Bannister CA, Holden SE, Jenkins-Jones S, Morgan CL, Halcox JP, Schernthaner G, Mukherjee J and Currie CJ. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. *Diabetes Obes Metab*. 2014;16:1165-73.

38. Coppe JP, Desprez PY, Krtolica A and Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol*. 2010;5:99-118.
39. Singh M, Jensen MD, Lerman A, Kushwaha S, Rihal CS, Gersh BJ, Behfar A, Tchkonia T, Thomas RJ, Lennon RJ, Keenan LR, Moore AG and Kirkland JL. Effect of Low-Dose Rapamycin on Senescence Markers and Physical Functioning in Older Adults with Coronary Artery Disease: Results of a Pilot Study. *J Frailty Aging*. 2016;5:204-207.
40. Lexis CP, van der Horst IC, Lipsic E, Wieringa WG, de Boer RA, van den Heuvel AF, van der Werf HW, Schurer RA, Pundziute G, Tan ES, Nieuwland W, Willemsen HM, Dorhout B, Molmans BH, van der Horst-Schrivers AN, Wolffenbuttel BH, ter Horst GJ, van Rossum AC, Tijssen JG, Hillege HL, de Smet BJ, van der Harst P, van Veldhuisen DJ and Investigators G-I. Effect of metformin on left ventricular function after acute myocardial infarction in patients without diabetes: the GIPS-III randomized clinical trial. *JAMA*. 2014;311:1526-35.
41. Rey-Valzacchi GJ, Costanzo PR, Finger LA, Layus AO, Gueglio GM, Litwak LE and Knoblovits P. Addition of metformin to sildenafil treatment for erectile dysfunction in eugonadal nondiabetic men with insulin resistance. A prospective, randomized, double-blind pilot study. *J Androl*. 2012;33:608-14.
42. Tso LO, Costello MF, Albuquerque LE, Andriolo RB and Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2014:CD006105.
43. Kordes S, Pollak MN, Zwinderman AH, Mathot RA, Weterman MJ, Beeker A, Punt CJ, Richel DJ and Wilmink JW. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol*. 2015;16:839-47.
44. Preiss D, Lloyd SM, Ford I, McMurray JJ, Holman RR, Welsh P, Fisher M, Packard CJ and Sattar N. Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *Lancet Diabetes Endocrinol*. 2014;2:116-24.
45. El Messaoudi S, Nederlof R, Zuurbier CJ, van Swieten HA, Pickkers P, Noyez L, Dieker HJ, Coenen MJ, Donders AR, Vos A, Rongen GA and Riksen NP. Effect of metformin pretreatment on myocardial injury during coronary artery bypass surgery in patients without diabetes (MetCAB): a double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2015;3:615-23.
46. Katz S, Ford AB, Moskowitz RW, Jackson BA and Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. *Jama*. 1963;185:914-9.
47. Scarpello JH and Howlett HC. Metformin therapy and clinical uses. *Diab Vasc Dis Res*. 2008;5:157-67.
48. Bailey CJ and Turner RC. Metformin. *The New England journal of medicine*. 1996;334:574-9.
49. Konopka AR, Esponda RR, Robinson MM, Johnson ML, Carter RE, Schiavon M, Cobelli C, Wondisford FE, Lanza IR and Nair KS. Hyperglucagonemia Mitigates the Effect of Metformin on Glucose Production in Prediabetes. *Cell Rep*. 2016;15:1394-400.

Appendices:

Appendix 1

Contraindications, warnings, precautions, adverse reactions and overdosage of metformin.

(Sources:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020357s031,021202s016lbl.pdf
and
http://www.fda.gov/downloads/drugs/drugsafety/ucm494140.pdf)

CONTRAINDICATIONS

Metformin are contraindicated in patients with:

1. Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m .
2. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m is not recommended.
3. Known hypersensitivity to metformin hydrochloride.

4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

WARNINGS

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Metformin and by use of the minimum effective dose of Metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate

metabolism. In addition, Metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of Metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

PRECAUTIONS

General

Macrovascular Outcomes—There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Metformin or any other anti-diabetic drug.

Monitoring of renal function—Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Metformin. In patients with advanced age, Metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, Metformin should not be titrated to the maximum dose.

Before initiation of Metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Metformin discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition—Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)—Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, Metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states—Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Metformin therapy, the drug should be promptly discontinued.

Surgical procedures—Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake—Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Metformin.

Impaired hepatic function—Since impaired hepatic function has been associated with some cases of lactic acidosis, Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 levels—In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Metformin and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes—A patient with type 2 diabetes previously well controlled on Metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Metformin must be stopped immediately and other appropriate corrective measures initiated.

Hypoglycemia—Hypoglycemia does not occur in patients receiving Metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose—When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Metformin and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either Metformin or sulfonylurea monotherapy, combined therapy with Metformin and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy or metformin XR/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

ADVERSE REACTIONS

Table 11: Most Common Adverse Reactions (>5.0 Percent) in a Placebo- Controlled Clinical Study of metformin Monotherapy*		
Adverse Reaction	**metformin Monotherapy (n=141)**	**Placebo (n=145)**
	% of Patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

*Reactions that were more common in metformin than placebo treated patients.

In a US double-blind clinical study of metformin in patients with type 2 diabetes, a total of 141 patients received metformin therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin- than placebo-treated patients, are listed in Table 1.

Diarrhea led to discontinuation of study medication in 6% of patients treated with metformin. Additionally, the following adverse reactions were reported in □1.0 - □5.0% of metformin patients and were more commonly reported with metformin than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

OVERDOSAGE

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Appendix 2

Phone Prescreening Questions to Identify Patients Likely to Be Frail

1. Can you climb two flights of stairs without stopping to rest?
2. Do you have difficulty completing any of the following activities on your own?
    a. Preparing meals
    b. Feeding yourself
    c. Dressing
    d. Using the toilet
    e. Housekeeping
    f. Climbing stairs
    g. Bathing
    h. Walking
    i. Using transportation
    j. Getting in and out of bed
    k. Managing medications
3. Which of the following describes your living environment?
    a. House; apartment; assisted living; nursing home; other
4. Do you depend on any assistive devices such as a cane, wheelchair, braces, walker, or assistance from other people to perform activities important to you in your daily life?
5. Do you wear dentures?
6. Do you have hearing aids?

If the patient answers no to question 1 or yes to any items under question 2, or questions 4-6, then that is a marker of possible frailty. We will invite all patients for the baseline screening visit, if there are 3 or more positive answers that suggest markers of frailty.

Short Physical Performance Battery
1. Repeated Chair Stands

Instructions: Do you think it is safe for you to try and stand up from a chair five times without using your arms? Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I'll be timing you with a stopwatch. Are you ready? Begin

Grading: Begin stop watch when subject begins to stand up. Count aloud each time subject arises. Stop the stopwatch when subject has straightened up completely for the fifth time. Also stop if the subject uses arms, or after 1 minute, if subject has not completed rises, and if concerned about the subject's safety.. Record the number of seconds and the presence of imbalance.. Then complete ordinal scoring.

Time: _____sec (if five stands are completed)
Number of Stands Completed: 1 2 3 4 5
Chair Stand Ordinal Score: _____
0 = unable
1 = > 16.7 sec
2 = 16.6-13.7 sec
3 = 13.6-11.2 sec

4 = < 11.1 sec

2. Balance Testing

Begin with a semitandem stand (heel of one foot placed by the big toe of the other foot). Individuals unable to hold this position should try the side-by-side position. Those able to stand in the semitandem position should be tested in the full tandem position. Once you have completed time measures, complete ordinal scoring.

a. Semitandem Stand

Instructions: Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into semitandem position. Allow participant to hold onto your arms to get balance. Begin timing when participant has the feet in position and lets go.

Circle one number
2. Held for 10 sec
1. Held for less than 10 sec; number of seconds held _____
0. Not attempted

b. Side-by-Side stand

Instructions: I want you to try to stand with your feet together, side by side, for about 10 sec. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and let's go.

Grading
2. Held of 10 sec
1. Held for less than 10 sec; number of seconds held_____
0. Not attempted

c. Tandem Stand

Instructions: Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 sec. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and let's go.

Grading

2. Held of 10 sec
1. Held for less than 10 sec; number of seconds held_____
0. Not attempted

Balance Ordinal Score: _____
0 = side by side 0-9 sec or unable
1 = side by side 10, <10 sec semitandem 2 = semitandem 10 sec, tandem 0-2 sec
3 = semitandem 10 sec, tandem 3-9 sec
4 = tandem 10 sec

3. 8' Walk (2.44 meters)

Instructions: This is our walking course. If you use a cane or other walking aid when walking outside your home, please use it for this test. I want you to walk at your usual pace to the other end of this course (a distance of 8'). Walk all the way past the other end of the tape before you stop. I will walk with you. Are you ready?

Grading: Press the start button to start the stopwatch as the participant begins walking. Measure the time take to walk 8'. Then complete ordinal scoring.

Time: _____ sec
Gait Ordinal Score: _____
0 = could not do
1 = >5.7 sec (<0.43 m/sec)
2 = 4.1-6.5 sec (0.44-0.60 m/sec)
3 = 3.2-4.0 (0.61-0.77 m/sec)
4 = <3.1 sec (>0.78 m/sec)

Summary Ordinal Score: _____

Range: 0 (worst performance) to 12 (best performance). Shown to have predictive validity showing a gradient of risk for mortality, nursing home admission, and disability.

Reprinted from Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol Med Sci 1994; 49(2):M85-M94