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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
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CITIZEN PETITION

The undersigned submits this petition pursuant to the Food, Drug, And Cosmetic Act (21 USC sec. 301 et. seq.) and in accordance with the implementing regulations under 21 CFR 10.30 and 201.56 to revise the prescribing label for metformin. The revised label should remove the current creatinine-based contraindications, and instead rely on estimated glomerular filtration rate (eGFR) thresholds. There should be no contraindications to metformin use based on renal function in those with eGFR ≥60 ml/min/1.72 m^2. Metformin use should be continued in those with eGFR 45 to <60 ml/min/1.72 m^2, with monitoring renal function every 3 to 6 months. Metformin should be prescribed with caution in those with eGFR 30 to <45 ml/min/1.72 m^2, using a lower dose (up to half maximum dose), closely monitoring renal function (every 3 months). Metformin should be stopped when eGFR is <30 ml/min/1.72 m^2.

A. Action requested

The current label states that metformin is contraindicated in patients with "renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS)."

The current creatinine-based contraindications should be removed from the label and instead it should read:

1) No contraindications to metformin use based on renal function in those with eGFR ≥60 ml/min/1.72 m^2.
2) Continue metformin use in those with eGFR 45 to <60 ml/min/1.72 m^2, monitoring renal function every 3 to 6 months.

3) Prescribe metformin with caution in those with eGFR 30 to <45 ml/min/1.72 m^2, using a lower dose (up to half maximum dose), closely monitoring renal function (every 3 months). Avoid starting new patients on metformin at this eGFR level.
4) Stop metformin when eGFR is <30 ml/min/1.72 m^2.

B. Statement of grounds

1. Historical Perspective

Metformin was not approved in the U.S. until December of 1994 despite extensive use of biguanies in Europe since the 1950s, primarily because of the risk of lactic acidosis that occurred with phenformin. Indeed, a marked reduction in biguanide use occurred in Europe in the mid-1970s because phenformin, extensively adopted in clinical practice, was implicated in a number of fatal cases of this severe metabolic decompensation.[1] The association with lactic acidosis eventually led to its withdrawal from the market. Importantly, lactic acidosis with phenformin appears to occur approximately 10- to 20-times more frequently than with metformin.[2] In contrast to metformin, modestly raised phenformin concentrations may reduce peripheral glucose oxidation and enhance peripheral lactate production which can increase circulating lactate levels. In fact, phenformin levels correlate with lactate concentration whereas metformin levels do not.[3] In addition, about 10% of European Caucasians have an inherent defect in phenformin hydroxylation which may lead to drug accumulation and, as a result, elevated lactate levels.[4] This experience with phenformin resulted in cautious use of metformin in Europe. In the 1980s, the creatinine cut-points for contraindication to metformin were considered to be appropriate at 1.4 mg/dl in women and 1.5 mg/dl in men. This was based upon the calculated ability to remove 3 grams of metformin (an amount slightly beyond the maximum daily U.S. dose) at steady-state levels within 24-48 hours. In fact, the ability to comfortably remove the drug extends up to creatinine levels of 1.8-2.0 mg/dl, but the cut-points chosen were intentionally set lower to ensure that those patients who may be lost to follow-up and whose creatinine levels increase over time would not be at risk for appreciable drug accumulation.

2. Metformin Pharmacokinetics

The principal reason for carefully setting renal thresholds is that metformin is eliminated unchanged primarily by the kidneys. Thus, one of the most important risk factors for elevated metformin concentrations (which are proposed to lead to lactic acidosis) is the inability to clear the drug efficiently. Metformin has a 50-60% bioavailability and is absorbed mainly in the small intestine. It does not appear to bind appreciably to plasma proteins. The maximum plasma concentration is observed approximately 2 hours after oral dosing, typically reaching a Cmax of 1-2 µg/mL (~10 µmol/L). Metformin accumulates in the walls of the small intestine and salivary glands as well as in the kidney.[5] It has a plasma elimination half-life of 6.2 hours and is renally eliminated both by filtration and active tubular secretion.[6]

In careful experiments, Tucker and colleagues studied metformin kinetics in 4 healthy subjects and 12 individuals with Type 2 diabetes[7] and found plasma renal clearance of metformin highly correlated with creatinine clearance (CrCl, $r=0.85$, $p<0.001$). However, the relationship between physiological clearance of an actual oral dose and CrCl was much weaker ($r=0.66$, $P<0.01$). Therefore, the investigators postulated that other factors may impact on this relationship – perhaps gastrointestinal absorption of metformin in patients with renal failure and/or non-renal clearance of a small amount of the drug.

In another pharmacokinetic study, a single 850mg dose of metformin was given to 21 healthy individuals and 13 subjects with renal insufficiency (mild to severe).[8] In the control group (mean CrCl 112 ±8 ml/min), average renal metformin clearance was 636 (±84) ml/min, whereas in mild CKD (CrCl 61-90 mL/min; mean 73 ±7 ml/min) clearance was reduced at 384

±122 ml/min. The mean renal clearance of metformin was lower in subjects with moderate (CrCl 31-60 mL/min; mean 41 ±9) and severe (CrCl 10-30 mL/min; mean 22 ±6) CKD, measuring 108 ±57 and 130 ±90 ml/min, respectively. Similarly, maximum concentration and the area under the concentration-time curve were increased in individuals with moderate-severe CKD compared to those with mild CKD or normal renal function. Based on the regression analysis, both CrCl and age were found to be important predictors of metformin clearance. This study did not provide evidence for specific thresholds at which lactate production may begin to rise.

These reports have relied upon information derived from single doses of metformin which may not reflect chronic treatment pharmacokinetics. In contrast, few have assessed the impact of renal insufficiency on metformin clearance during long-term use. Indeed, one such study concluded that metformin can be efficiently cleared in mild-moderate CKD. In this investigation, 24 older patients (age 70-88) were administered metformin 850 mg/day or 1,700 mg/day based on CrCl of 30-60 ml/min (n=11) or >60 ml/min (n=13), respectively. After 2 months, metformin remained in the therapeutic range and lactate within the reference limits in all participants. In addition, the measured levels of metformin and lactate were not statistically different between those with and without renal impairment.[9]

Another recent study evaluated metformin levels in patients with Type 2 diabetes and varying renal function.[10] GFR was estimated based upon cystatin C levels. The median dose of metformin was 1,500 mg per day. The median serum level of metformin was 4.5 µmol/l (~0.6 µg/ml) (range 0.1-20.7 µmol/l) in patients with eGFR>60 ml/min/1.73m^2 (n=107), 7.71 µmol/l (~1.0 µg/ml) (range 0.12-15.15) with eGFR 30-60 (n=21), and 8.88 µmol/l (~1.1 µg/ml) (range 5.99-18.6) with eGFR<30 (n=9). Notably, there were wide variations in these levels within each group, with few patients having serum levels > 20 µmol/l (>~2.6 µg/ml). However, the metformin concentration that is 'unsafe' is not really known. At usual clinical doses and schedules, steady state plasma concentrations are generally <1 µg/ml (<7.8 µmol/l). Maximum plasma levels during controlled clinical trials do not generally exceed 5 µg/ml (38.8 µmol/l) – but these have not typically enrolled CKD patients. Moreover, whether measurement of metformin levels can actually aid in the prediction of lactic acidosis risk remains unclear. Therefore, while these studies provide us some information on the relationship between renal function and metformin concentrations, they do not clarify the issue of toxicity and lactic acidosis risk. Many of the early pharmacokinetic studies with metformin actually relied on CrCl based upon 24-hour urine collection for creatinine. How well the current serum creatinine cut-points reflect the ability to effectively clear the drug is also unknown. Creatinine levels, in general, vary inversely with GFR. However, important limitations to the estimation of renal function with creatinine should be considered. First, serum creatinine can only be used reliably in patients with stable kidney function. Second, variation in creatinine production may differ among and within individuals over time, especially if there are significant changes in muscle mass or in physical activity. Variability in creatinine secretion, extra-renal creatinine excretion, assay method, and equipment can all affect serum measurements. Calculated estimates (clearance from the Cockroft-Gault [CG] and eGFR from the Modification of Diet in Renal Disease [MDRD] equation) have been developed to incorporate known demographic and clinical factors affecting serum concentrations. These equations have their own inherent shortcomings, such as residual limitations with respect to age and race, underestimation of GFRin the context of diabetic renal disease (CG and MDRD)[11] and in obese individuals (MDRD)[12]. However, they provide better estimation of renal function than creatinine alone. Moreover, development of new estimating equations, such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), may allow for even more accurate estimates of renal function in the future. Finally, dosing considerations by the FDA for other medications (e.g.

sitagliptin, fenofibrate) are now generally based upon CrCl estimated from such calculations and *not* on creatinine levels themselves.

3. Lactic Acidosis Associated with Metformin Therapy

Even though elevated metformin concentrations have been proposed to lead to lactic acidosis, there are actually few data regarding the level predisposing to hyperlactatemia. In fact, multiple studies suggest that elevated circulating lactate levels, often attributed to metformin, may actually not be caused by the drug. First, lactic acidosis occurs in patients with Type 2 diabetes more frequently than in the general population; in some reports the observed rate appears to be similar in patients on metformin versus other glucose-lowering agents.[13] Secondly, metformin and lactate levels do not necessarily appear to correlate, such that higher metformin concentrations do not consistently occur in those with more severe degrees of lactic acidosis.[14, 15] Lastly, metformin levels are not linked to mortality in those who develop lactic acidosis, perhaps reflecting the primary effect of the underlying cause of the acidosis (e.g., hypoxia, hemodynamic compromise) on outcomes, rather than incriminating metformin itself.[14-16]

Although lactic acidosis remains a recognized, albeit rare, adverse event associated with metformin, the number of lactic acidosis cases continues to be very small, particularly when one considers the widespread use of this drug. In the largest updated Cochrane meta-analysis, Salpeter *et al.* pooled data from 347 comparative trials and cohort studies.[17] Not a single case of lactic acidosis was found in >70,000 metformin patient-years or > 55,000 non-metformin person-years. In this analysis, 53% of prospective studies allowed for inclusion of renal insufficiency, but patient-level serum creatinine concentrations were not available for review. Based upon statistical inference, the estimated upper limit of true incidence was 4.3 and 5.4/100,000 patient-years in the metformin and non-metformin groups, respectively. This investigation suggests that lactic acidosis is extremely rare and the incidence does not differ in those treated with metformin versus other agents.

In a large nested-case control analysis of the UK general practice research database, the crude incidence of lactic acidosis was even lower at 3.3/100,000 person-years among metformin users and 4.8 among sulfonylurea users[13] (in very close agreement to the estimates of 3 and 2.4 cases/100,000 patient-years from Europe and Scandinavia before metformin's U.S. approval). Given all of these findings, some have argued that the occurrence of lactic acidosis with metformin use is merely coincidental and that there is no tangible evidence from prospective observational studies or clinical trials that the drug increases its incidence.[18] Of course, all these data have been collected in the context of contemporaneous strict metformin prescribing guidelines. Conceivably, looser restrictions may have lead to more frequent occurrence of lactic acidosis.

In summary, lactic acidosis remains exceedingly rare in clinical trials and cohort studies of metformin therapy. Moreover, the available data suggest that lactate levels and risk of lactic acidosis do not differ appreciably in patients taking this versus other glucose-lowering agents. Thus, the long-proclaimed causal relationship between metformin and lactic acidosis remains in question.

4. Evidence Based on Current Use of Metformin in CKD

Given the current contraindications in the U.S., some might consider it a challenge to conduct a new clinical trial to evaluate the use of metformin in individuals with various degrees of impaired renal function, taking account new criteria for assessing glomerular filtration. Yet, evidence suggests that metformin is often already used in practice outside of the current labeling contraindications, prescribed in full knowledge of the relevant cut-offs.[19-22] For

example, in a review of restrictions to metformin therapy conducted in Scotland, 24.5% of metformin users had filled a prescription despite an active contraindications (3.4% had the specific local exclusion of a serum creatinine ≥1.7mg/dL recorded twice on different days within 4 weeks).[22] A single case of lactic acidosis during 4,600 patient-years of follow-up occurred in a patient with an extensive acute myocardial infarction who developed acute renal failure and died the same day. Given the clinical scenario, the authors intimated that acidosis had occurred because of hemodynamic compromise related to the infarct and not to metformin accumulation. In a U.S. study performed in the primary care practice setting, 4.5% of patients treated with metformin had creatinine levels above 1.4-1.5 mg/dL in men and women, respectively.[23] Two other studies of sicker patients admitted to hospitals in Germany and the US confirmed high frequency of metformin use despite various contraindications (27% and 73% respectively).[19, 21]

When one considers the imperfect reflection of actual renal function by serum creatinine, metformin is likely used even more frequently in patients with impaired GFR than that suggested by the above studies. In the aforementioned U.S. primary practice setting where 4.5% were given metformin despite creatinine-based contraindications, 17.7% of women and 13.4% of men receiving metformin actually had an abnormally low eGFR (<60 ml/min/1.73m^2).[23] Similarly, in another single U.S. center cross-sectional study, 15.3% of patients with Type 2 diabetes and eGFR< 60 ml/min/1.73m^2 were receiving metformin. Such frequent 'inappropriate' use of metformin in patients is further suggested by data from the National Health and Nutrition Examination Survey (NHANES, 1999-2006). Among individuals with eGFR <60 ml/min/1.73m^2 and diabetes, 32.2% were treated with metformin and had a normal creatinine (<1.5 mg/dl), whereas 13.4% were treated with metformin despite a frankly elevated creatinine (>1.5 mg/dl). The use of metformin in mild-moderate CKD is clearly not at all uncommon.

Two studies have attempted to translate creatinine into corresponding eGFR cut-points in the context of metformin therapy. In a review of prescribing practices in the U.K., appropriate use of the drug was defined based upon creatinine ≤1.7mg/dl.[24] Out of 11,297 patients meeting those criteria, 82% had an eGFR<90, 25.5% <60, and 2.8% <30 ml/min/1.73m^2. The authors calculated that the eGFR threshold of 36 ml/min would result in a similar number of patients becoming ineligible for metformin compared to the serum creatinine threshold of 1.7 mg/dl (although some patients would become newly *eligible* and some who previously qualified would now become *ineligible*). The authors proposed that if the current practice is considered 'safe' (and based upon Salpeter's review this appears to be so), then a switch to an eGFR-based cut-point may be both a more practical and a more accurate way to limit metformin access in those with significantly impaired renal function. In another British study of 12,482 patients with diabetes, an eGFR cut-off of 41 ml/min/1.73m^2 in males and 30 ml/min/1.73m^2 in females resulted in a similar proportion of patients having metformin withheld compared to the serum creatinine threshold of 1.7 mg/dl. The investigators therefore proposed the pragmatic eGFR limit of 30 ml/min/1.73m^2 to denote absolute contraindication to therapy.[25]

Until recently, there were limited data specifically addressing metformin's long-term safety in patients with mild-moderate renal failure.[26-28] These studies found no increased risks in various degrees of renal insufficiency, but were limited by small size and significant methodological shortcomings. Recently, two large studies have provided evidence about the safety and effectiveness of metformin use in patients with CKD. The analysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry suggests that the proposed cardiovascular benefits of metformin may extend to patients with established atherosclerosis and moderate CKD.[29] In this large observational study of over 19,000 subjects with a history of atherothrombotic disease, 1,572 patients were using metformin with eGFR 30-60

ml/min/1.73m^2. After adjustment for baseline factors and propensity score, metformin use was associated with a significant reduction in 2-year mortality in the overall population (HR 0.76, 95% CI 0.65-0.89), including in those with moderate CKD (HR 0.64, 95% CI 0.48-0.86). However, lack of information with respect to the duration of metformin use and HbA1c, as well as the observational nature of the study, require further confirmation of the mortality benefit in similar patient cohorts in prospective trials. In the large National Diabetes Registry analysis in Sweden, the use of metformin, insulin, or other oral agents were compared after propensity score adjustment among >50,000 patients with type 2 diabetes with respect to cardiovascular outcomes, acidosis/serious infection, and all-cause mortality[30]. Metformin use was associated with reduced risk of cardiovascular disease, acidosis/serious infection, and all-cause mortality compared with insulin and a reduced risk of all-cause mortality compared with other oral agents. The effect was consistent in patients with mildly reduced renal function (eGFR 45-60 ml/min/1.73m^2) and there we no increased risk of acidosis/serious infection in patients with moderate CKD (eGFR 30-45 ml/min/1.73m^2). Although the analysis was adjusted by propensity scores, confounding by indication could still be present. Moreover, patients who changed their therapy during the study were not censored. Finally, analysis of lactic acidosis was limited by the occurrence of only eight cases (however, unless these were under-diagnosed or not properly coded, this provides added reassurance).

Although these data are reassuring, we must note that there are no randomized clinical trials which specifically evaluated the safety of metformin use and potential cardiovascular benefits in patients with CKD.

5. Current Clinical Guidelines Already Endorse GFR-based Contraindications

The prescribing information for metformin in the current label is explicit with respect to renal contraindications, based on serum creatinine cut-points. It proscribes use at or above the 1.4 - 1.5 mg/dl levels in women and men, respectively. Yet, several U.S. practice guidelines substantially differ in their recommendations for metformin use related to renal status. A consensus statement authored by members of the ADA and European Association for the Study of Diabetes (the EASD), reports that metformin appears safe unless eGFR falls below 30 ml/min/1.73m^2.[31] The recent position statement of the ADA and EASD endorses GFR-based guidelines consistent with NICE:

"In the U.K., the National Institute for Health and Clinical Excellence (NICE) guidelines are less proscriptive and more evidence-based than those in the U.S., generally allowing use down to a GFR of 30 mL/min, with dose reduction advised at 45 mL/min. Given the current widespread reporting of estimated GFR, these guidelines appear very reasonable."

Clinical guidelines outside of the U.S. already incorporate the eGFR for determination of metformin safety. In the U.K., for example, prescribing guidelines consider both creatinine and eGFR for assessing treatment eligibility. The National Institute for Health and Clinical Excellence (NICE) recommends to review the clinical circumstances when serum creatinine exceeds 130 µmol/L (1.5 mg/dL) *or* eGFR falls below 45 mL/min/1.73m^2. NICE further specifies that metformin be stopped if serum creatinine exceeds 150 µmol/L (1.7 mg/dl) (a higher threshold than in the U.S.) *or* eGFR is below 30 ml/min/1.73m^2.[32] In contrast, the Canadian Diabetes Society practice guidelines are now based solely on eGFR, recommending caution with eGFR <60 ml/min/1.73m^2 and contraindicating its use with eGFR <30 ml/min/1.73m^2.[33] The Australian Diabetes Society practice guidelines similarly recommend against metformin with eGFR <30 ml/min/1.73m^2 and caution with eGFR 30-45 ml/min/1.73m^2.[34] Thus, while there is clear recognition that renal failure may be a risk factor for adverse events with metformin use, there is significant divergence in opinion across the globe regarding the optimal definition of safety.

6. Advantages of Metformin

Metformin is safe, effective, inexpensive, and has a favorable side effect profile. There is also some evidence that early treatment with metformin is associated with reduced cardiovascular morbidity and total mortality in newly diagnosed type 2 diabetic patients[35]. In contrast, despite multiple trials of intensive glucose control using a variety of glucose lowering strategies, there is a paucity of data to support specific advantages with other agents on cardiovascular outcomes.

Unlike sulfonylureas, thiazolidinediones, and insulin, metformin is weight neutral[36], which makes it an attractive choice for obese patients. Furthermore, the management of type 2 diabetes can be complicated by hypoglycemia, which can seriously limit the pursuit of glycemic control. Here, too, metformin has advantages over insulin and some types of insulin secretagogues; by decreasing excess hepatic gluconeogenesis without raising insulin levels, it rarely leads to significant hypoglycemia when used as a monotherapy[13, 35]. As a result, metformin is widely considered an ideal first-line agent for the treatment of type 2 diabetes, as recommended by several clinical guidelines[32, 37].

7. Summary of Evidence Supporting Change in Metformin Label

In summary, we recommend that the current creatinine-based contraindications to metformin therapy be replaced with GFR-based guidelines, consistent with the NICE guidelines. These recommendations are based on better estimation of renal function with GFR compared to creatinine and metformin's continued record of safety with respect to lactic acidosis risk.

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C. Environmental impact

There is no expected impact on the environment based on this petition.

D. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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E. Additional Signatures

The petition was circulated to clinical leaders involved in care of patients with diabetes and was signed electronically by the following 111 individuals who supported the petition:

Date / Time Signed	Name and Degrees	Affiliation
Feb 15, 2013 3:32 PM	Virginia Peragallo-Dittko, RN, BC-ADM, CDE, FAADE	Executive Director, Winthrop-University Hospital Diabetes and Obesity Institute Mineola, NY
Feb 10, 2013 2:59 PM	Joseph Tibaldi, MD	Queens Diabetes and Endocrine Associates Physician, Ass Clinical Prof, Cornell
Feb 10, 2013 12:12 PM	Satish Garg MD	Professor of Medicine and Pediatrics, Editor-in-Chief, *Diab Tech & Ther* University of Colorado Denver

Feb 8, 2013 4:58 PM	Samuel Dagogo-Jack, MD	Professor of Medicine & Director Division of Endocrinology, Diabetes & Metabolism A. C. Mullins Chair in Translational Research Director, General Clinical Research Center Director, Endocrinology Fellowship Training Program University of Tennessee Health Science Center Memphis, TN
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Feb 8, 2013 12:04 AM	Steven E. Kahn, M.B., Ch.B.	Professor of Medicine University of Washington
Feb 7, 2013 4:41 PM	James Sowers MD	Professor of Medicine University of Missouri, Columbia Mo.
Feb 7, 2013 4:08 PM	Richard Nesto MD FACC FAHA FRCP (lLondon and Edin.)	Lahey Health Executive VP and CMO Professor, Tufts University School of Medicine
Feb 7, 2013 6:58 AM	Robin Goland, MD	Professor, Columbia University Co-Director, Naomi Berrie Diabetes Center
Feb 7, 2013 4:49 AM	Mikhail Kosiborod, MD	Associate Professor of Medicine, St. Luke's Mid America Heart Institute, University of Missouri Kansas City
Feb 7, 2013 4:12 AM	Barbara I. Gulanski, MD, MPH	VA Connecticut Healthcare System Chief, Section of Endocrinology
Feb 6, 2013 7:41 PM	Craig Williams, PharmD, FNLA, BCPS	Associate Professor College of Pharmacy, Oregon Health & Science Univ former member, ADA Professional Practice Committee
Feb 6, 2013 6:25 PM	Margo Farber, PharmD	Director, Drug Information Service University of Michigan Health System
Feb 6, 2013 6:08 PM	Jennifer Marks, MD	University of Miami School of Medicine, Diabetes Research Institute
Feb 6, 2013 6:07 PM	Paul J. Beisswenger MD	Geisel School of Medicine at Dartmouth Professor of Medicine and Endocrinology
Feb 6, 2013 5:31 PM	Mark Feinglos, MD, CM	Professor of Medicine, Division of Endocrinology, Duke University Medical Center
Feb 6, 2013 5:06 PM	Deborah Hinnen APRN, BC-ADM, CDE, FAAN, FAADE	Director, Education Services Mid America Diabetes Associates Wichita, KS
Feb 6, 2013 3:39 PM	Chirag Parikh, MD, PhD	Associate Professor, Section of Nephrology, Yale University School of Med
Feb 6, 2013 3:31 PM	Davida F. Kruger, MSN, APN-BC,BC-ADM	Nurse practitioner Henry Ford Health System, Detroit, MI
Feb 6, 2013 3:14 PM	Marjorie Cypress PhD, CNP, CDE	ABQ Health Partners Nurse Practitioner, Dept Endocrinology and Diabetes
Feb 6, 2013 2:46 PM	Rajesh Garg, MD	Assistant Professor of Medicine, Harvard Medical School
Feb 6, 2013 2:41 PM	Martha Funnell, MS, RN, CDE	Diabetes Educator University of Michigan
Feb 6, 2013 2:34 PM	Elizabeth A. Walker, PhD, RN	Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY
Feb 6, 2013 2:24 PM	Mercedes Falciglia, MD	Associate Professor of Medicine University of Cincinnati College of Medicine Cincinnati VAMC
Feb 6, 2013 2:13 PM	Allison B. Goldfine, MD	Associate Professor, Harvard Medical School Head Section of Clinical Research, Joslin Diabetes Center, Boston, MA
Feb 6, 2013 1:28 PM	William T. Cefalu, M.D.	Professor of Diabetes Pennington Biomed Research Center, Baton Rouge, LA
Feb 6, 2013 1:17 PM	Bruce W. Bode, MD FACE	President, Atlanta Diabetes Associates Associate Professor of Medicine, Emory University School of Medicine
Feb 6, 2013 12:53 PM	Carole Mensing, RN, MA,CDE	ADA Professional Volunteer & Past Officer

Feb 6, 2013 12:35 PM	Graham McMahon, M.D., M.M.Sc	Associate Professor of Medicine, Harvard Medical School; Diabetologist, Brigham and Women's Hospital, Boston, MA
Feb 6, 2013 11:17 AM	John E. Anderson, MD	President, Medicine and Science The American Diabetes Association
Feb 6, 2013 5:14 AM	Chalak Muhammad, MD, MPH, CDE	Physician; Diabetologist
Feb 6, 2013 4:31 AM	Janet McGill, MD, MA	Professor of Medicine Washington University School of Medicine
Feb 5, 2013 2:10 PM	Carlos Mendez, MD	Director Diabetes Management Program Stratton VA Medical Center
Feb 5, 2013 4:30 AM	Kenneth Cusi, MD, FACP, FACE	Professor of Medicine and Chief, Endocrinology, Diabetes and Metabolism Division, University of Florida
Feb 3, 2013 9:06 PM	Robert Vigersky, M.D.	Director, Diabetes Institute Walter Reed National Military Medical Center
Feb 2, 2013 11:21 PM	Daniel Einhorn, MD	Clinical Professor, UC San Diego
Feb 1, 2013 9:25 PM	Gretchen Youssef, MS, RD, CDE	MedStar Diabetes Institute, MedStar Health Washington, DC
Feb 1, 2013 2:52 AM	Ellie Strock ANP-BC, CDE	Adult nurse practitioner, International Diabetes Center Minneapolis, MN
Jan 31, 2013 11:50 PM	Richard Wender M.D.	Alumni Professor and Chair Department of Family and Community Medicine Thomas Jefferson University, Philadelphia, PA
Jan 31, 2013 10:49 PM	Alan R. Shuldiner, MD	University of Maryland School of Medicine John Whitehurst Professor of Medicine
Jan 31, 2013 7:10 PM	John R. White, Jr., PA-C, Pharm.D,	Interim Chairman and Professor Dept. of Pharmacotherapy, College of Pharmacy Washington State University Spokane
Jan 31, 2013 7:02 PM	Michael Bergman, MD	Clinical Professor of Medicine NYU School of Medicine
Jan 31, 2013 3:31 PM	Rebecca R. Brothers, Pharm.D., BCPS	Assistant Chief, Clinical Programs VAMC Cincinnati,
Jan 31, 2013 1:52 PM	Paul Callaway, MD, FAAFP	Program Director Wesley Family Medicine Residency Program Clinical Professor University of Kansas School of Medicine-Wichita
Jan 31, 2013 1:19 PM	Clifford J Bailey, PhD, FRCP(Edin), FRCPath	Professor of Clinical Science Aston University, Birmingham
Jan 31, 2013 9:42 AM	Yehuda Handelsman, MD	Chair, Diabetes Scientific Committee, AACE
Jan 30, 2013 11:09 PM	Kieren Mather, MD	Associate Professor of Medicine Indiana University School of Medicine
Jan 30, 2013 10:17 PM	Mayer B. Davidson, MD	Charles R. Drew University Director, Diabetes Program Martin Luther King-Multiservice Ambulatory Care Center
Jan 30, 2013 8:48 PM	Zachary Bloomgarden, MD	Editor, *The Journal of Diabetes* Clinical Professor Department of Medicine, Mount Sinai School of Medicine
Jan 30, 2013 5:27 PM	Matthew Riddle, MD	Professor of Medicine Division of Endocrinology, Diabetes, & Clinical Nutrition Oregon Health & Science University, Portland, Oregon
Jan 30, 2013 4:45 PM	Scott R Drab BS, PharmD, CDE, BC-ADM	Director, University Diabetes Care Associates Univ of Pittsburgh
Jan 30, 2013 4:23 PM	Abbas Kitabchi, PhD, MD, FACP, FACE	University of Tennessee Health Science Center Division of Endocrinology, Diabetes, & Metabolism
Jan 30, 2013 4:22 PM	Edward S. Horton, MD	Senior Investigator, Joslin Diabetes Center Professor of Medicine, Harvard Medical School
Jan 30, 2013 4:07 PM	Mary Korytkowski MD	Interim Chief, Division of Endocrinology School of Medicine, University of Pittsburgh

Jan 30, 2013 3:43 PM	Eugene J. Barrett, M.D., Ph.D.	Professor of Medicine, Diabetes Center Director University of Virginia
Jan 30, 2013 3:40 PM	Ralph A DeFronzo, M.D.	Professor of Medicine University of Texas Health Science Center at San Antonio
Jan 30, 2013 2:16 PM	Darren K. McGuire, MD, MHSc	Associate Professor of Medicine Director, Parkland Hospital and Health System Outpatient Cardiology Clinics University of Texas Southwestern Medical Center Dallas, Texas
Jan 30, 2013 2:12 PM	Belinda Childs APRN, MN	MidAmerica Diabetes Associates, PA Director: Clinical and Research Services
Jan 30, 2013 2:01 PM	Stanley Schwartz MD	Affiliate, Main Line Health System Emeritus, Clinical Assoc. Prof of Medicine Univ of Pa.
Jan 30, 2013 1:30 PM	George Bakris, MD	Professor of Medicine, Director, ASH Comprehensive Hypertension Center, The University of Chicago Medicine
Jan 30, 2013 11:04 AM	John M Miles, MD	Professor of Medicine Mayo Clinic
Jan 30, 2013 6:35 AM	Jeff Unger, MD	Director, Metabolic Studies Catalina Research Institute President, Unger Primary Care Center
Jan 30, 2013 3:57 AM	Joel Zonszein, MD, CDE, FACP, FACE	Director, Clinical Diabetes Center Professor of Clinical Medicine Montefiore Medical Center Albert Einstein College of Medicine Bronx, New York
Jan 30, 2013 3:46 AM	Thomas A. Buchanan, MD	Professor of Medicine, Division of Endocrinology and Diabetes, Keck School of Medicine of the University of Southern California
Jan 30, 2013 3:13 AM	Carol H. Wysham, MD	Clinical Associate Professor of Medicine University of Washington School of Medicine
Jan 30, 2013 2:33 AM	Geralyn R Spollett, MSN, ANP-CS, CDE	Yale Diabetes Center Associate Director and Nurse Practitioner
Jan 30, 2013 2:15 AM	David K. McCulloch, BSc, MB, CHB, MD, FRCP	Diabetologist, Group Health Cooperative, Clinical Professor of Medicine, University of Washington
Jan 30, 2013 12:56 AM	Sunder Mudaliar, MD	Staff Physician, Diabetes/Endocrinology University of California, San Diego
Jan 30, 2013 12:27 AM	Richard M. Bergenstal, MD	Executive Director, International Diabetes Center Minneapolis, MN Past President, Medicine and Science American Diabetes Association
Jan 29, 2013 11:52 PM	Richard J. Comi, MD	Professor of Medicine Geisel School of Medicine Fellowship Director Endocrine Fellowship Dartmouth Hitchcock Medical Center
Jan 29, 2013 10:32 PM	Ronald Goldberg MD	Professor of Medicine Division of Endocrinology, Diabetes and Metabolism Diabetes Research Institute University of Miami Miller School of Medicine
Jan 29, 2013 9:12 PM	Guillermo Umpierrez, MD	Professor of Medicine Emory University
Jan 29, 2013 9:06 PM	Kathleen Dungan, MD, MPH	The Ohio State University Division of Endocrinology, Diabetes & Metabolism Assistant Professor of Medicine
Jan 29, 2013 8:27 PM	Marc J Laufgraben, MD, MBA	Associate Professor of Medicine Cooper Medical School of Rowan University Division Head Division of Endocrinology, Diabetes and Metabolism Cooper University Health Care
Jan 29, 2013 8:15 PM	Daniel Lorber, MD, FACP, CDE	Director of Endocrinology New York Hospital Queens

Jan 29, 2013 7:48 PM	Robert J. Rushakoff, MD	Professor of Medicine Director for Inpatient Diabetes Endocrinology and Metabolism University of California, San Francisco
Jan 29, 2013 7:44 PM	Steven Wittlin MD	U of Rochester Medical Center Director of Diabetes Services Clinical Director of Endocrinology
Jan 29, 2013 7:34 PM	Anthony L. McCall MD, PhD, FACP	James M. Moss Professor of Diabetes University of Virginia School of Medicine
Jan 29, 2013 7:18 PM	Eliot A. Brinton, MD	President, Utah Lipid Center Salt Lake City, Utah
Jan 29, 2013 7:16 PM	Jaime A. Davidson, MD, FACP, MACE	Clinical Professor of Medicine Division of Endocrinology, Diabetes and Metabolism Touchstone Diabetes Center The University of Texas Southwestern Medical Center
Jan 29, 2013 6:58 PM	Robert Henry, MD	Professor of Medicine, University of California San Diego and Chief, Section of Diabetes, Endocrinology & Metabolism, VA San Diego Healthcare System
Jan 29, 2013 6:43 PM	George Grunberger, MD	Chairman, Grunberger Diabetes Institute Clinical Professor, Internal Medicine and Molecular Medicine & Genetics, Wayne State University School of Medicine
Jan 29, 2013 6:37 PM	Adrian Vella MD	Professor of Medicine Division of Endocrinology & Metabolism Mayo Clinic Rochester MN
Jan 29, 2013 6:22 PM	Andrew Ahmann, MD	Director, Harold Schnitzer Diabetes Health Center Oregon Heatlh and Science University
Jan 29, 2013 6:12 PM	Richard Pratley, MD	Director, Florida Hospital Diabetes Institute
Jan 29, 2013 6:11 PM	Serge Jabbour, MD, FACP, FACE	Professor of Medicine Director, Division of Endocrinology, Diabetes & Metabolic Diseases Jefferson Medical College of Thomas Jefferson University Philadelphia, PA
Jan 29, 2013 6:08 PM	John L. Leahy, MD	Chief Division of Endocrinology, Diabetes and Metabolism, and Professor of Medicine, University of Vermont.
Jan 29, 2013 6:03 PM	David Rodbard MD	Biomedical Informatics Consultants LLC
Jan 29, 2013 6:03 PM	Robert J Tanenberg, MD, FACP	Professor of Medicine Director, Diabetes Clinical Research Center Division of Endocrinology Director, Diabetes Fellowship Brody School of Medicine Medical Director, Diabetes and Obesity Institute East Carolina University
Jan 29, 2013 6:01 PM	Luigi Meneghini, MD, MBA	University of Miami Miller School of Medicine Professor of Clinical Medicine
Jan 29, 2013 5:58 PM	Derek LeRoith MD PhD	Mt Sinai School of Medicine and Hospital Professor of Medicine
Jan 29, 2013 5:55 PM	Jay S. Skyler, MD, MACP	Professor of Medicine - University of Miami Deputy Director for Clinical & Academic Affairs, Diabetes Research Institute, University of Miami
Jan 29, 2013 5:53 PM	Alan Garber MD PhD	Professor of Medicine, Biochemistry and Cell Biology, Baylor College of Medicine
Jan 29, 2013 5:47 PM	Charles Burant, MD, PhD	Professor of Internal Medicine University of Michigan
Jan 29, 2013 5:38 PM	Philip Raskin, MD	Professor of Medicine The University of Texas, Southwestern Medical Center Dallas, Texas

Jan 29, 2013 5:35 PM	Boris Draznin, MD, PhD	Director, Adult Diabetes Program, University of Colorado Denver School of Medicine
Jan 29, 2013 5:34 PM	Robert H. Eckel, MD	University of Colorado Anschutz Medical Campus Endocrinologist, Diabetologoist, Lipid Specialist
Jan 29, 2013 5:15 PM	Anne Peters, MD	Director, USC Clinical Diabetes Programs Professor, Keck School of Medicine of USC
Jan 29, 2013 5:02 PM	David M. Nathan, MD	Director, Diabetes Center Massachusetts General Hospital Professor of Medicine Harvard Medical School
Jan 29, 2013 4:14 PM	M. Sue Kirkman, MD	Professor of Medicine University of North Carolina
Jan 29, 2013 4:09 PM	John Buse, MD, PhD	Professor of Medicine, Chief of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, NC
Jan 29, 2013 4:07 PM	Vivian Fonseca MD	Tulane University Past President, American Diabetes Association
Jan 29, 2013 3:42 PM	Kevin O'Brien, MD	Prof. of Medicine Div. of Cardiology University of Washington
Jan 29, 2013 3:41 PM	Mark E. Molitch, M.D.	Martha Leland Sherwin Professor of Endocrinology Division of Endocrinology, Metabolism & Molecular Medicine Department of Medicine Northwestern University Feinberg School of Medicine
Jan 29, 2013 3:35 PM	David Baldwin MD	Director: Section of Endocrinology Rush University Medical Center Chicago, IL
Jan 29, 2013 3:30 PM	Irl Hirsch, MD	Professor of Medicine, University of Washington School of Medicine. Medical Director, Diabetes Care Center, University of Washington Medical Center
Jan 29, 2013 3:30 PM	Faramarz Ismail-Beigi, MD, PhD	Case Western Reserve University Professor of Medicne (Endocrinology)
Jan 29, 2013 3:29 PM	Etie Moghissi, MD, FACE	Clinical Associate Professor Medicine , University of California, Los Angeles.
Jan 29, 2013 3:25 PM	Franco Folli MD PhD	Professor of Medicine Diabetes Division, Department of Medicine University of Texas Health Science Center at San Antonio
Jan 29, 2013 3:18 PM	David D'Alessio, MD	Professor of Medicine Director, Division of Endocrinology University of Cincinnati and Cincinnati VAMC

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