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Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy

George Bakris[1], Ellen Burgess[2], Matthew Weir[3], Giora Davidai[4] and Stephen Koval[4], on behalf of the AMADEO Study Investigators[5]

[1]Department of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois, USA; [2]Division of Nephrology, Department of Medicine, University of Calgary, Calgary, Canada; [3]Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA and [4]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, USA

In patients with diabetic nephropathy, lowering blood pressure and reducing proteinuria by over 30% correlates with a slower progression to kidney failure. We compared two different angiotensin receptor-blockers in a double blind, prospective trial of 860 patients with type 2 diabetes whose blood pressure levels was over 130/80 mmHg or who were receiving antihypertensive medication(s) and who had a morning spot urinary protein to creatinine ratio of 700 or more. Patients were randomized to telmisartan (a highly lipophilic agent with a long half-life) or losartan (with low lipophilicity and short half-life). The primary endpoint was the difference in the urinary albumin to creatinine ratio between the groups at 52 weeks. The geometric coefficient of variation and the mean of the urinary albumin to creatinine ratio fell in both groups at 52 weeks but both were significantly greater for the telmisartan compared to the losartan cohort. Mean systolic blood pressure reductions were not significantly different between groups at trial end. We conclude that telmisartan is superior to losartan in reducing proteinuria in hypertensive patients with diabetic nephropathy, despite a similar reduction in blood pressure.

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Correspondence: *George Bakris, Department of medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637-5415, USA. E-mail: gbakris@medicine.bsd.uchicago.edu*

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[5]A complete list of the AMADEO Investigators can be found in the APPENDIX.

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Proteinuric kidney disease is a frequent complication of diabetes, the most common cause of kidney failure in the western world,[1] and results in reduced life expectancy.[2] *Post hoc* analyses of renal outcome trials demonstrate that a >30% reduction in proteinuria at 6 months correlates with slowed progression of kidney disease.[3–6] Uncontrolled hypertension contributes to increases in proteinuria, and blood pressure control is associated with reduced urinary protein excretion and slowed decline in renal function.[7] Achievement of a target blood pressure, that is, <130/80 mm Hg, in patients with proteinuria, using a blocker of the rennin–angiotensin system as part of the regimen, is recommended by current guidelines.[8–10] The current trial tests the hypothesis that a highly lipophilic[11] angiotensin-receptor blocker (ARB) with a long half-life will yield relatively greater antiproteinuric effects at similar levels of blood pressure control compared with one that has a shorter half-life and low lipophilicity.

RESULTS

This prospective, randomized, double-blind, double-dummy, forced-titration, multicenter, parallel-group, study compared telMisartan (80 mg) vs losArtan (100 mg) in hypertensive type-2 DiabEtic patients with Overt nephropathy. It was conducted at 124 centers in Argentina, Australia, Brazil, Canada, Mexico, New Zealand, South Korea, Taiwan, Thailand, and the United States, with 1,567 outpatients meeting inclusion criteria and 860(55%) randomized to treatment (Table 1). There were many reasons for people not being randomized and most dealt with problems related to duration of follow-up and frequency of visits. Eighty percent of the total cohort completed the trial, 345 and 342 patients in the telmisartan and losartan groups, respectively. The mean duration of follow-up for the entire cohort was 324.25 days.

Primary endpoint

Although each agent reduced adjusted mean urinary protein-to-creatinine (UPC) significantly (29.8% telmisartan

Table 1 | Baseline characteristics of randomized AMADEO patients[+]

	Telmisartan 80-mg regimen (*n*=419)	Losartan 100-mg regimen (*n*=441)
Age (years)	60.0 ± 9.2	60.5 ± 9.4
<65 years (%)	66.8	62.1
Male (%)	61.1	63.3
Ethnicity (%)		
Caucasian	44.9	49.2
Black	14.1	9.8
Asian	41.1	40.8
Missing	0	0.1
Mean ± s.d. BMI (kg/m^2)	30.1 ± 6.8[a]	29.9 ± 6.2[b]
Current smokers (%)	15.0	16.1
Ex-smokers (%)	38.7	39.8
Duration of hypertension (years)	9.0 ± 8.9[a]	9.6 ± 9.4[b]
Duration of diabetic nephropathy (years)	2.5 ± 3.7[c]	2.3 ± 3.5[d]
Duration of type-2 diabetes (years)	14.6 ± 8.4	14.1 ± 8.1
Urinary protein:creatinine (mg/g creatinine)$^{++}$	1970.9 (100.8%)[e]	2010.5 (104.5%)[f]
Urinary albumin:creatinine (mg/g creatinine)$^{++}$	1400.8 (118.0%)[g]	1387.0 (126.0%)[h]
Urinary sodium:creatinine (mmol/g creatinine)$^{++}$	72.4 (95.1%)[e]	76.7 (88.4%)[h]
Serum creatinine (mg/dl)$^{++}$	1.54 (40.6%)	1.55 (41.2%)
eGFR (ml/min/1.73 m^2)	49.5 ± 21.6	49.6 ± 22.4
Serum aldosterone (ng/dl)$^{++}$	7.6 (91.9%)[i]	7.1 (90.8%)[j]
C-reactive protein (mg/l)$^{++}$	2.2 (209.5%)[a]	2.4 (197.9%)[b]
SBP (mm Hg)	143.7 ± 15.7	143.2 ± 15.4
DBP (mm Hg)	79.9 ± 9.4	79.5 ± 9.6
Hemoglobin A1c (%)	7.9 ± 1.3[g]	7.9 ± 1.3[h]

AMADEO, a prospective, randomized, double-blind, double-dummy, forced-titration, multicenter, parallel-group, 1-year treatment trial to compare telMisartan (80 mg) vs losArtan (100 mg) in hypertensive type-2 DiabEtic patients with Overt nephropathy; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; gCV, geometric mean of variation; gMean, geometric mean; SBP, systolic blood pressure; s.d., standard deviation.
[+]All values are expressed as mean ± s.d.
[a]*n*=418.
[b]*n*=439.
[c]*n*=417.
[d]*n*=438.
[e]*n*=413.
[f]*n*=437.
[g]*n*=411.
[h]*n*=435.
[i]*n*=402.
[j]*n*=428.

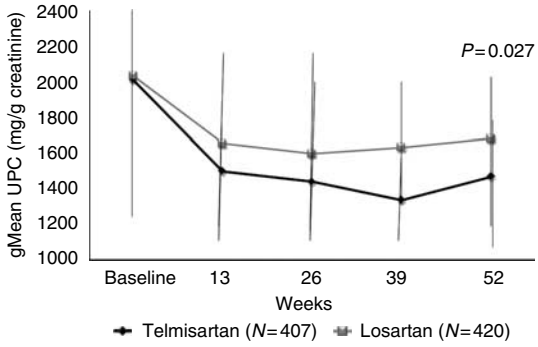

Figure 1 | Changes in UPC in each group. The values represent mean ± s.d.s at each time point.

($P<0.0001$) and 21.4% losartan ($P<0.0001$)), the reduction in UPC from baseline was greater for telmisartan ($P=0.03$; Figure 1), thus achieving the primary endpoint.

Secondary endpoints

Table 2 summarizes secondary endpoints. In the telmisartan group, the geometric mean urinary albumin:creatinine was reduced from 1426.1 mg/g to 952.5 mg/g creatinine ($P<0.0001$). In the losartan group, the corresponding values for baseline and end of treatment were 1,390.5 and 1,054.9 mg/g creatinine ($P<0.0001$). This translated into a 35.5% greater reduction with telmisartan vs 27.0% with losartan ($P=0.04$). These between-proteinuria differences could not be accounted for by differences in sodium intake throughout the trial (Figure 2).

Changes in blood pressure are shown in Figure 3. Both groups had significant reductions in diastolic pressure at trial end, with no differences between groups (3.3 ± 0.6, telmisartan vs 2.9 ± 0.6, losartan; $P=0.61$). Systolic pressure also failed to show consistent difference throughout the study (Figure 3). There was a trend in favor of telmisartan on the day-56 time point, where a 4.2-mm Hg difference was present favoring telmisartan, although much smaller differences were seen at all other time points throughout the remainder of the study (Figure 3). Note that during the initial washout period, all patients had their angiotensin-converting enzyme inhibitors (47.3%, telmisartan and 43.8% losartan groups) and ARBs (20.5% telmisartan and 23.8% losartan groups) stopped. Antihypertensive agents that were continued into the randomized phase included calcium-channel blockers (71.5%), thiazide diuretics (64.7%), and β-blockers (47.0%). Note that more than 80% of the calcium-channel blockers were in the dihydropyridine subclass and there were no differences in use between the groups. Other agents continued into the randomized phase were oral antidiabetic agents (66.0%), statins (56.9%), and insulin (47.3%), with no differences in use between treatment groups. Moreover, during the trial agents that were added to achieve blood pressure or metabolic control to those receiving only randomized drugs included dihydropyridine calcium-channel blockers (76.4%), diuretics (74.2%), β-blockers (53.5%), oral antidiabetic agents (70.5%), statins (64.5%), and insulin (54.3%), with no differences between treatment groups.

There were no between-group differences in the time to first event for the secondary composite endpoints of doubling of serum creatinine, end-stage renal disease, and all-cause death (14 events (3.4%), telmisartan vs 25 events (5.9%), losartan; $P=0.083$). The composite renal endpoint alone was not different between the groups. A between-group difference for the composite of cardiovascular morbidity or mortality, however, was noted (21 events, telmisartan vs 37 events, losartan; $P=0.037$). All-cause death was also different between groups (2 events, telmisartan vs 13 events, losartan; $P=0.007$).

Table 2 | Change from baseline in secondary renal endpoints at 1 year

Endpoint	Telmisartan 80-mg regimen[a]	Losartan 100-mg regimen[a]	*P*-value
Serum creatinine (mg/dl)	15% (12%, 18%)	15% (12%, 18%)	0.8950
eGFR (ml/min/1.73 m^2)	–6.49 (–7.56, –5.42)	–6.50 (–7.56, –5.43)	0.9913
Serum aldosterone (ng/dl)	–23% (–29%, –18%)	–17% (–23%, –11%)	0.0746
C-reactive protein (mg/dl)	–6% (–15%, 4%)	1% (–9%, 13%)	0.2777

eGFR, estimated glomerular filtration rate.
[a]Adjusted percentage change from baseline (95% confidence interval) for all endpoints except for eGFR, which was given as the adjusted mean change from baseline (95% confidence interval).

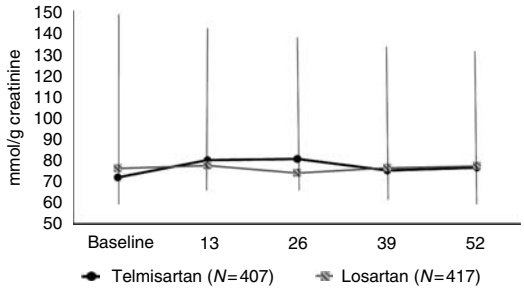

Figure 2 | Changes in urinary sodium excretion as assessed by spot sodium:creatinine at each time point when proteinuria data were collected. The values represent mean ± s.d.s at each time point.

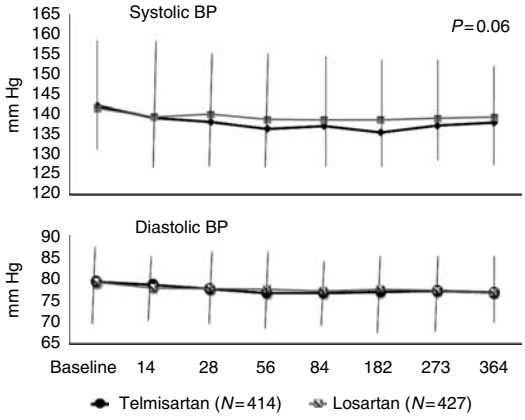

Figure 3 | Changes in systolic and diastolic blood pressure in each group. The values represent mean ± s.d.s at each time point.

Safety

Adverse events were experienced by 84% of the telmisartan-group patients and 82.1% of the losartan-group patients. Severe events were recorded in 15.5% of the telmisartan- and 22.4% of the losartan-group patients. Hyperkalemia was rare in the study, with 1.8% of the total cohort having a serum potassium level of >5.5 mEq/l. There were six discontinuations in each group due to treatment-related adverse events. During the study, 25 patients died, but no death was considered study drug-related.

DISCUSSION

The results of this trial demonstrate that in patients with hypertension and diabetic nephropathy, a telmisartan-based regimen is superior to a losartan-based regimen for reducing proteinuria, given similar levels of blood pressure reduction at 1 year. This change in proteinuria was based on a change in spot urine protein:creatinine. This method overcomes the drawbacks of 24-h urine collection[12] and correlates with such values in different patient groups;[13,14] thus, it is a recommended method for clinical trials.[15,16]

There are many factors that affect proteinuria and may have influenced the results, although most of those did not account for differences seen in this trial. One possible factor that could have affected proteinuria is a disproportionate increase in dietary sodium intake in one group, since this is known to blunt the antiproteinuric effects of the renin–angiotensin system blockers.[17] However, we detected no differences between groups in sodium excretion as assessed by spot urinary sodium:creatinine ratio at any time point where proteinuria was assessed. Thus, in this study, changes in proteinuria cannot be attributed to differences in dietary sodium.

Another possible explanation for these between-group differences in proteinuria could relate to a lower blood pressure favoring one group. Differences in diastolic blood pressure were not present at any time during the trial. A trend for a lower systolic pressure, however, was present in the telmisartan group early in the trial, but failed to reach significance at trial end. Moreover, the greatest difference in systolic blood pressure was noted on day 56, where the difference between groups was 2.9 mm Hg. At every other time point, non-significant differences of <2 mm Hg in systolic pressure were observed. There are also no outcome trial data to support the concept that a 2- or 3-mm Hg difference in systolic blood pressure translates into proteinuria differences. Data from the Captopril trial demonstrated that a 4-mm Hg difference in systolic blood pressure was significant between the groups and translated into a proteinuria difference.[18] Thus, since the magnitude of blood pressure change in this trial is less than that, it probably does not account for this difference. An additional issue related to blood pressure lowering maybe the type of agents added to one group favoring further reduction in proteinuria. This was also not the case, since all additional antihypertensive agents were used to a similar extent between the groups.

Another possible explanation for differences between groups relates to the *in vitro* demonstration that telmisartan stimulates peroxisome proliferator-activated receptor-γ activity. Such agents used for diabetes treatment also lower

proteinuria and blood pressure independent of other antihypertensive agents.[19] Unfortunately, the activity of the peroxisome proliferator-activated receptor-γ observed *in vitro* with telmisartan has not been shown to translate into any clinically apparent effect on insulin resistance.[20]

Angiotensin-1-receptor binding differences between ARBs could also be conjectured to account for differences in outcome, although we did not measure such binding in this trial. It is clear that telmisartan has a higher affinity for the angiotensin-1 receptor and has a significantly greater percentage of binding compared with losartan.[21,22] Whether this translates into a better antiproteinuric effect, however, remains to be proven.

Other factors known to affect proteinuria, such as a greater reduction in estimated glomerular filtration rate or serum aldosterone were also not different between groups. Additionally, dropout rates were similar between groups due to the incidence of adverse events. As an example, the incidence of hyperkalemia defined as a serum potassium of >5.5 mEq/l between groups was 1.8% for the study overall, with no difference between groups. Thus, both telmisartan and losartan were relatively well tolerated and safe. It, therefore, appears that there is no clear explanation for these proteinuria differences.

Losartan has approval by the Food and Drug Administration for slowing diabetic nephropathy, based on the results of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study.[23] In the RENAAL study, proteinuria was reduced by 29% at 6 months and correlated with significant slowing of nephropathy progression compared with placebo.[24] Moreover, *post hoc* analysis of the RENAAL trial showed that losartan-induced changes in proteinuria were more predictive of renal outcomes than blood pressure changes.[25] In this study, the proteinuria reduction observed with the losartan regimen was 21.4 vs 29.8% with a telmisartan regimen. In both treatment groups, the greatest reduction in proteinuria was apparent during the first 26 weeks and persisted for the remainder of the trial. Similar trends were also observed for albuminuria. In a separate study, the rate of progression from micro- to macro-albuminuria in patients with type-2 diabetes was reduced by telmisartan.[26] This anti-albuminuric effect of telmisartan was independent of blood pressure level, as transition rates were reduced in both hypertensive ($>140/90$ mm Hg) and normotensive patients.

We conclude that a telmisartan-based regimen for blood pressure reduction provides robust antiproteinuric effect in hypertensive patients with nephropathy-associated type-2 diabetes. This antiproteinuric effect is greater than a losartan-based regimen at levels of blood pressure that were not different. Based on available trial data, this difference in antiproteinuric effect may translate into better renal and cardiovascular outcomes. Long-term outcome studies, such as ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), will demonstrate whether the antiproteinuric effect of telmisartan is associated with a reduction in cardiovascular events in high-risk patients.[27]

MATERIALS AND METHODS

Study design

This is a prospective, randomized, double-blind, double-dummy, forced-titration, multicenter, parallel-group study. After a 4-week placebo washout period, with discontinuation of any ARB, angiotensin-converting enzyme inhibitor, or direct vasodilator, eligible patients were randomized to telmisartan or losartan treatment. During the first 2 weeks, the once-daily dose of telmisartan was 40 mg and 50 mg for losartan. For the remaining 50 weeks, the doses of telmisartan and losartan were 80 and 100 mg/day, respectively. Additional antihypertensive medication (excluding other ARBs, angiotensin-converting enzyme inhibitors, or direct vasodilators) could be given following forced titration to achieve the blood pressure targets ($<130/80$ mm Hg).

Study population

Inclusion criteria were as follows: (1) age 21–80 years, (2) history of type-2 diabetes mellitus, (3) total hemoglobin A1c $\leqslant 10\%$, (4) serum creatinine $\leqslant 3$ mg/dl (women) or $\leqslant 3.2$ mg/dl (men), and (5) first-morning spot UPC $\geqslant 700$ mg/g creatinine. Note that urinalysis was performed to eliminate the possibility of other abnormalities such as hematuria and so on. Lastly, mean systolic blood pressure and/or diastolic blood pressure 130/80 mm Hg, or receiving antihypertensive(s) for hypertension. If systolic blood pressure exceeded 160 mm Hg or diastolic blood pressure exceeded 110 mm Hg at any time, patients were automatically withdrawn. Blood pressure was assessed using the American Heart Association criteria.[9] Exclusion criteria included (1) women who were nursing, pregnant, or surgically sterile and not using effective contraception; (2) $>35\%$ increase in serum creatinine during the washout period or serum potassium level >5 mEq/l; (3) non-diabetic renal disease; (4) clinically significant heart disease, stroke, renal artery stenosis, hepatic dysfunction, or electrolyte imbalance; (5) known hypersensitivity to any component of the study medications; and (6) requiring chronic immunosuppressive therapy.

Study endpoints

The primary efficacy endpoint was change from baseline in early-morning spot UPC. Secondary renal endpoints included change from baseline in early-morning spot albumin:creatinine; estimated glomerular filtration rate, using the modified MDRD equation;[28] and early-morning spot sodium:creatinine. Also, a composite of a doubling of serum creatinine concentration, end-stage renal disease (need for long-term dialysis, renal transplantation, or a serum creatinine $\geqslant 6$ mg/dl), or death was assessed. Other secondary endpoints were change from baseline in systolic blood pressure and diastolic blood pressure, high-sensitivity C-reactive protein, and serum aldosterone. Adverse events and safety laboratories were also monitored. All samples were stored at –20 °C and dispatched to a central laboratory (Quest Diagnostics Clinical Trials, Van Nuys, CA, USA) for analysis.

Statistical analysis

The power of the study was assessed assuming a standard deviation of the change from baseline in UPC from similar cohorts observed in different trials, and expected to be approximately 2 mg/g creatinine.[29,30] Thus, 340 patients per treatment arm would yield

90% power at the 5% (two-sided) level of significance to detect a between group difference of 0.5 mg/g creatinine in UPC in the reduction from baseline. We further assumed, however, a 15% dropout rate with no final UPC measurement; consequently, 400 patients per treatment arm were required to identify any differences in efficacy.

Efficacy was determined in patients with a baseline and $\geqslant 1$ on-treatment renal efficacy parameter measurement, with last observation carried forward. For the primary endpoint, an analysis of covariance that included treatment and pooled center as class effects, with baseline as a covariate, was performed on the log-transformed data. Mean values were expressed as geometric means (geometric coefficient of variation, %). Significance of changes from baseline within treatment groups and differences between treatment groups were established by two-sided 95% confidence interval and *P*-value. The same procedure was used for all secondary renal endpoints other than estimated glomerular filtration rate, which were expressed as arithmetic mean and standard deviation. Changes in blood pressure were expressed as mean values and standard error. Time-to-event data were analyzed by Kaplan–Meier method, with treatment groups being compared by means of log-rank test. Baseline demographics were summarized descriptively for each treatment.

DISCLOSURE

All the authors declared no competing interests.

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APPENDIX

Investigators

Argentina: Mario Bendersky, Betina Bustos, Betina, Alberto Caccavo, Emilo Kuschnir, Jorge Lowenstein, Silvia Nicolai, Ernesto Paolasso, Siliva Saavedra, Ramiro Sanchez, Jorge Thierer. Australia: William Jeffries, Garry Jennings, Jeff Karrasch; Brazil: Fernando Almeida, João Felício, Adriana

Forti, Roberto Franco, Rosângela Milagres, Rogério Paula, Artur Ribeiro, José Saraiva; Canada: Ronnie Aronson, Gordon Bailey, Paul Barré, Sabyasachi Bose, Ellen Burgess, Richard Dumas, Jean-Marie Ekoe, Thomas Elliott, Richard Goluch, Irving Gottesman, Sita Gourishankar, Jean-Pierre Halle, Gavril Hercz, Shivinder Jolly, Phillip McFarlane, Theodore Monchesky, Liam Murphy, Tewfik Nawar, Malvinder Parmar, Robert Petrella, Stuart Ross, Luis Salgado, Robert Schlosser, Jay Silverberg, Steven Soroka, Hugh Tildesley, Yaw Twum-Barima, Deborah Zimmerman; Mexico: Ernesto Cardona, Jaime Illescas, Norberto Matadamas, Eduardo Meaney, José Parra, Rogelio Peralta, Jesús Rivera, Ignacio Rodriguez, Jorge Torres Gutierrez, Sergio Trevethan; New Zealand: Ajith Dissanayake, Russell Scott; South Korea: Chul Woo Ahn, Hye-Soon Kim, Young Duk Song. Taiwan: Chien-Wen Chou, Shinn-Tzon Gong, Tien-Shang Huang, Yi-Jen Hung, Tin-Kwang Lin, Ji-Hung Wang; Thailand: Ampica Mangklabruks, Thongchai Pratipanawatr, Nopawan Kittivat, Prasart Laothavorn, Peera Buranakitjaroen, Suthon Porntisan; USA: Spiros Arbes, Habib Azad, George L Bakris, Thomas Berl, DeAnna E Cheek, Jhoong Cheigh, William H Cleveland, Debbie Cohen, Dalila B Corry, Troy E Dixon, Steven Fishbane, Linda Fried, Francis Gabbai, Leland E Garrett Jr, Michael Germain, Jesse Mark Goldman, Stephen Graham, Syed A Hussain, Kambiz Kalantarinia, Mark S Kipnes, Michael Krishnan, Cheryl Laffer, Sam Lerman, Barton Levine, Harold R Locay, Rafael A Lopez, Laura Lyngby Mulloy, Leonard G Meggs, James H Mersey, Sylvia D Noble, Ernesto Perez, Pablo E Pergola, Velvie Anne Pogue, German Ramirez, Philip Raskin, Efrain Reisin, Paul D Schneider, Steven Schwartz, Craig A Shadur, Mary Jo Shaver, Harmeet Singh, Richard Solomon, Bruce S Spinowitz, Chao Sun, Vinay A Sunku, Manuel Velasques, Donald G Vidt, Cristovao Vieira, Mark Williams, Bessie A Young, Steven Zeig.