Supplemental Digital Content

Manuscript Title: Association of Arterial pH with Hemodynamic Response to Vasopressin in Patients with Septic Shock: An Observational Cohort Study

Authors: Seth R. Bauer, Gretchen L. Sacha, Matthew T. Siuba, Simon W. Lam, Anita J. Reddy, Abhijit Duggal, Vidula Vachharajani

Table of Contents

e-Table 1. Sensitivity Analyses of Alternative Methods to Calculate Arterial pH From Venous pH and Restricted Sample

Analysis method[a]	Vasopressin Hemodynamic Response OR (95% CI) per 0.1 unit pH below 7.40[b]	Vasopressin Hemodynamic Response OR (95% CI) per 0.1 unit pH below 7.40[c]
Primary method[d]	0.72 (0.66-0.79)	0.79 (0.72-0.87)
Alternate method 1[e]	0.72 (0.66-0.79)	0.79 (0.72-0.87)
Alternate method 2[f]	0.73 (0.67-0.79)	0.80 (0.72-0.88)
Alternate method 3[g]	0.72 (0.66-0.79)	0.79 (0.72-0.87)
Restricted sample[h]	0.74 (0.67-0.81)	0.81 (0.73-0.91)

[a]Each analysis method, except the restricted sample analysis, had 297 arterial pH values calculated from venous pH values as described and 1053 pH values from arterial samples.

[b]Univariate logistic regression

[c]Multivariable logistic regression adjusted for lactate concentration and Sequential Organ Failure Assessment score at vasopressin initiation

[d]Arterial pH values calculated from venous pH values by adding 0.04 to venous pH to equate to arterial pH (per Kelly 2001)[1]

[e]Arterial pH values calculated from venous pH values by adding 0.034 to venous pH to equate to arterial pH (per Kelly 2002)[2]

[f]Arterial pH values calculated from venous pH values with the following equation: arterial pH = -0.307 + (1.05*venous pH) (per Treger 2010)[3]

[g]Arterial pH values calculated from venous pH values by adding 0.03 to venous pH to equate to arterial pH (per Adrogué 1989 and Middleton 2006)[4,5]

[h]Study sample restricted to only those 1053 patients with an arterial value pH available

e-Table 2. Sensitivity Analysis of Alternative Norepinephrine-Equivalent Catecholamine Dose Equivalence

Characteristic[a]	Total (N=1350)	pH ≤7.19 (n=325)	pH 7.20-7.29 (n=359)	pH 7.30-7.39 (n=421)	pH ≥7.40 (n=245)	p
NE-equivalent catecholamine dose change at 1 hour after vasopressin start (mcg/min)[b]	-0.6 ± 24.3	2.9 ± 32.3	-1.1 ± 30.7	-1.6 ± 13.3	-2.9 ± 13.1	<0.01
NE-equivalent catecholamine dose change at 3 hours after vasopressin start (mcg/min)[b]	-0.1 ± 27.8	4.8 ± 34.1	-0.9 ± 32.8	-1.8 ± 18.7	-2.4 ± 22.8	<0.01
NE-equivalent catecholamine dose change at 6 hours after vasopressin start (mcg/min)[b]	-0.8 ± 32.4	4.9 ± 40.6	-2.1 ± 36.4	-2.5 ± 23.5	-3.5 ± 25.6	<0.01
MAP/NEQ change at 1 hour after vasopressin start (mm Hg/mcg/kg/min)[c]	29 (-16, 103)	9 (-28, 60)	21 (-27, 91)	40 (-1, 121)	56 (-5, 166)	<0.01
MAP/NEQ change at 3 hours after vasopressin start (mm Hg/mcg/kg/min)[c]	30 (-35, 128)	3 (-47, 83)	27 (-44, 125)	38 (-17, 136)	56 (-30, 264)	<0.01
MAP/NEQ change at 6 hours after vasopressin start (mm Hg/mcg/kg/min)[c]	38 (-44, 184)	13 (-68, 132)	37 (-50, 178)	41 (-29, 187)	86 (-18, 355)	<0.01

[a]Norepinephrine-equivalent catecholamine doses in mcg/min were calculated as [norepinephrine (mcg/min)] + [epinephrine (mcg/min)] + [dopamine (mcg/kg/min)*weight(kg)/100] + [phenylephrine (mcg/min)/10] (per Goradia 2021)[6]

[b]Data presented as mean ± standard deviation

[c]Data presented as median (interquartile range)

e-Table 3. Subgroup Analysis of Patient Outcomes by Clinical pH Group at Vasopressin Initiation in Medical Intensive Care Unit Patients

Characteristic	Total (N=880)	pH ≤7.19 (n=209)	pH 7.20-7.29 (n=235)	pH 7.30-7.39 (n=268)	pH ≥7.40 (n=168)	p
Primary outcome						
Hemodynamic response[a]	432 (49.1)	69 (33.0)	114 (48.5)	145 (54.1)	104 (61.9)	<0.01
Odds ratio (95% CI)[b]		0.41 (0.26-0.65)	0.66 (0.44-1.0)	0.80 (0.53-1.19)	1 (referent)	
Secondary outcomes						
NE-equivalent catecholamine dose change at 1 hour after vasopressin start (mcg/min)	-0.2 ± 28.5	+4.6 ± 37.8	-1.4 ± 37.1	-1.8 ± 14.3	-2.2 ± 13.9	<0.01
NE-equivalent catecholamine dose change at 3 hours after vasopressin start (mcg/min)	+1.5 ± 25.9	+7.8 ± 34.2	+2.4 ± 26.9	-1.5 ± 18.6	-2.8 ± 20.7	<0.01
NE-equivalent catecholamine dose change at 6 hours after vasopressin start (mcg/min)	+1.0 ± 28.7	+8.0 ± 35.4	+1.0 ± 27.5	-1.9 ± 24.0	-2.9 ± 26.7	<0.01
MAP/NEQ change at 1 hour after vasopressin start (mm Hg/mcg/kg/min)[c]	23 (-20, 86)	6 (-28, 53)	21 (-26, 81)	34 (-4, 95)	37 (-10, 131)	<0.01
MAP/NEQ change at 3 hours after vasopressin start (mm Hg/mcg/kg/min)[c]	22 (-36, 115)	3 (-42, 61)	12 (-49, 118)	35 (-21, 111)	38 (-31, 213)	<0.01
MAP/NEQ change at 6 hours after vasopressin start (mm Hg/mcg/kg/min)[c]	36 (-44, 158)	9 (-72, 116)	26 (-57, 153)	48 (-25, 162)	57 (-36, 228)	0.03
28-Day mortality	595 (67.6)	166 (79.4)	157 (66.8)	165 (61.6)	107 (63.7)	<0.01[d]

Data presented as n (%) or mean ± standard deviation, unless otherwise specified

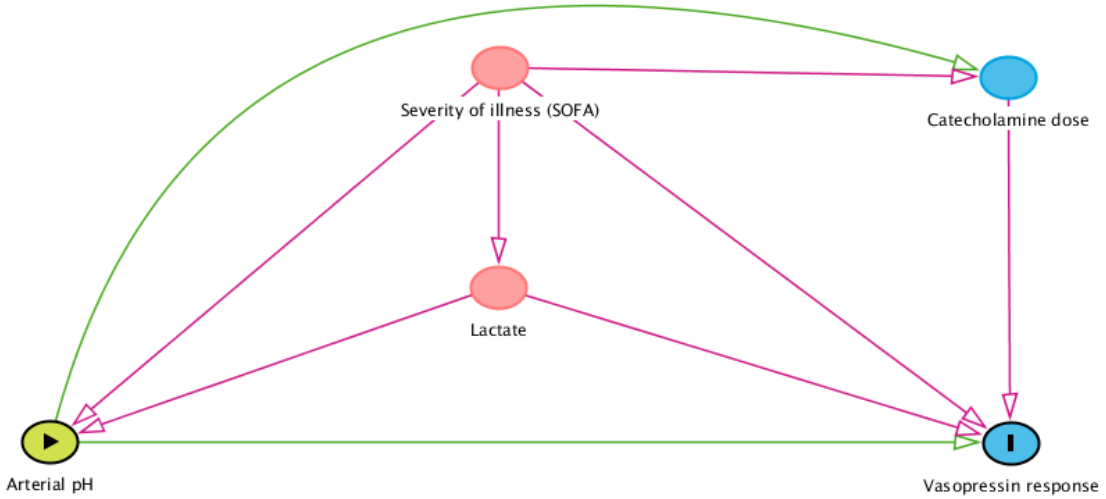
[a]On univariate logistic regression, as arterial pH decreased the odds of hemodynamic response to vasopressin decreased (for each 0.1 unit arterial pH was below 7.40, response OR 0.71; 95% CI 0.64-0.79, P<0.01)

[b]Odds ratio and 95% CI from multivariable logistic regression analysis adjusted for lactate concentration and sequential organ failure assessment at vasopressin initiation

[c]Presented as median (interquartile range)

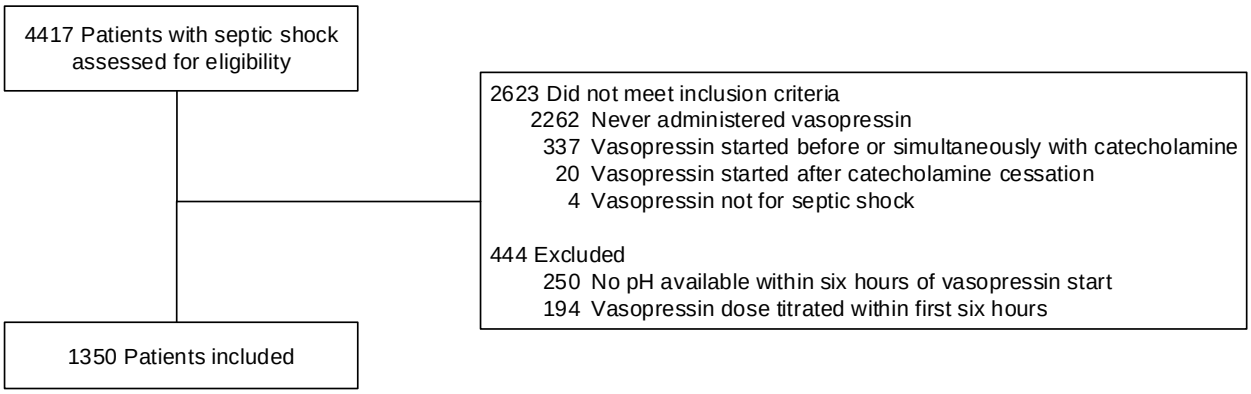
[d]For the comparison of the pH ≤7.19 group to the pH ≥7.40 group, $HR(t) = e^{[0.69-0.11*t]}$; at t=0, HR 1.99, 95% CI 1.42-2.78

e-Figure 1. Directed Acyclic Graph for Variable Selection in Multivariable Model for Vasopressin Hemodynamic Response

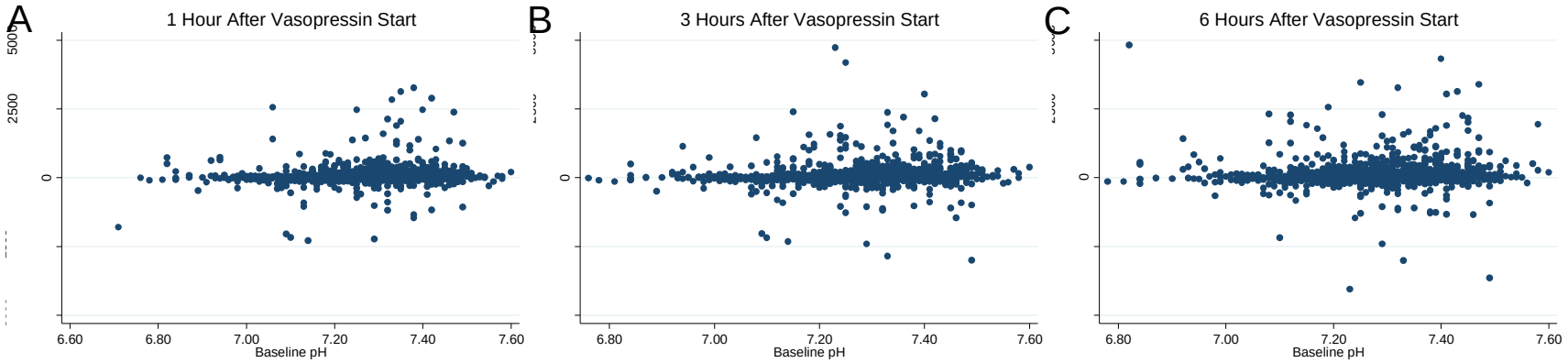


SOFA = Sequential Organ Failure Assessment score

e-Figure 2. Patient Flow Diagram

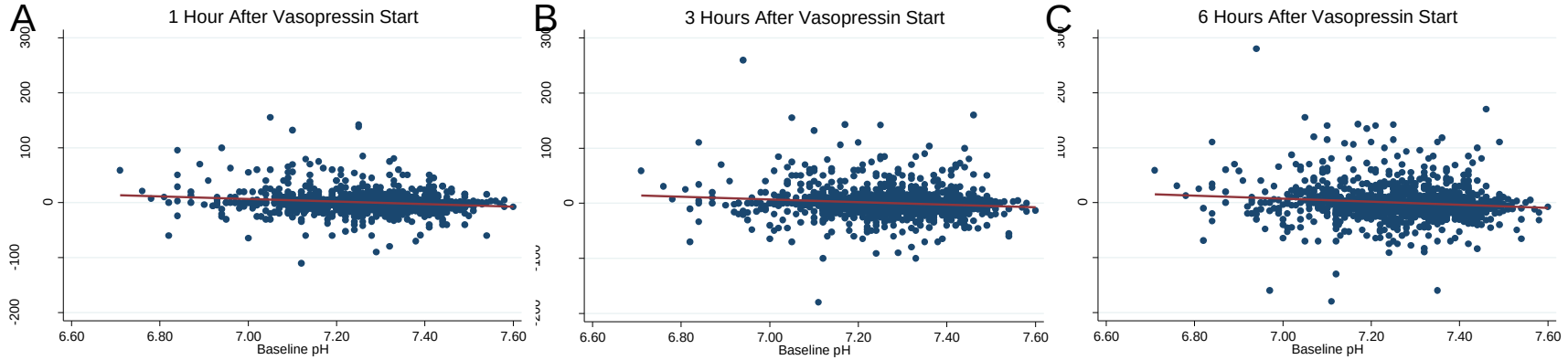


e-Figure 3. Change in Ratio of Mean Arterial Pressure to Norepinephrine-Equivalent Catecholamine Dose After Vasopressin Start by pH



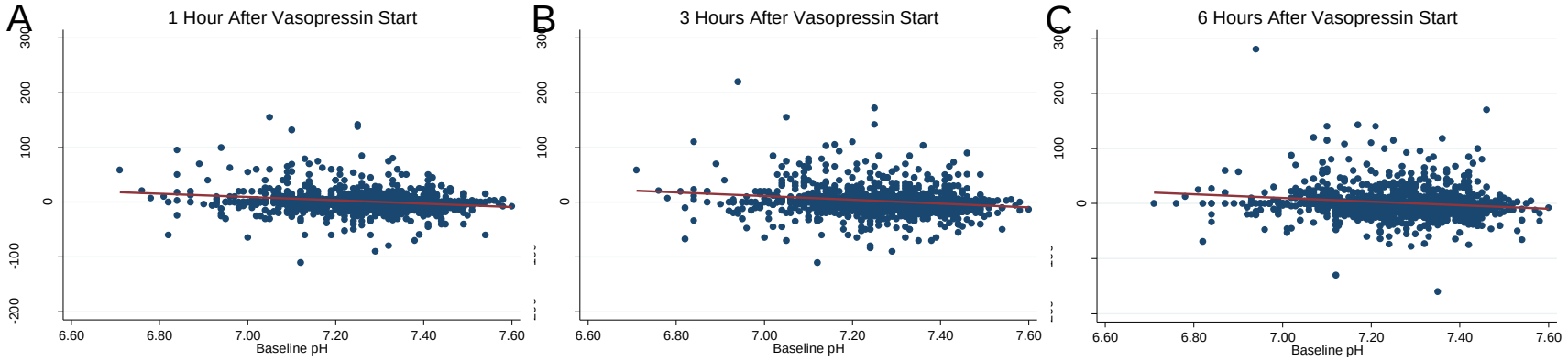
Change in MAP/NEQ at one hour (A; n=1227), three hours (B; n=1192), and at six hours (C; n=1133) after vasopressin start by arterial pH at vasopressin initiation. MAP/NEQ = mean arterial pressure/norepinephrine-equivalent catecholamine dose.

e-Figure 4. Sensitivity Analysis of Change in Norepinephrine-Equivalent Catecholamine Dose After Vasopressin Start by pH Using Alternative Dose Equivalence



Change in norepinephrine-equivalent catecholamine dose at one hour (A; n=1350), three hours (B; n=1345), and at six hours (C; n=1344) after vasopressin start by arterial pH at vasopressin initiation. Lines represent the predicted change in norepinephrine-equivalent catecholamine dose from a linear regression of norepinephrine-equivalent catecholamine dose on arterial pH at vasopressin initiation. Norepinephrine-equivalent catecholamine doses in mcg/min were calculated as [norepinephrine (mcg/min)] + [epinephrine (mcg/min)] + [dopamine (mcg/kg/min)*weight(kg)/100] + [phenylephrine (mcg/min)/10].[6] For each 0.1 unit the pH was below 7.40 at vasopressin initiation, the norepinephrine-equivalent catecholamine dose increased by 1.5 mcg/min (95% CI 0.5-2.5 mcg/min) at one hour, increased by 2.3 mcg/min (95% CI 1.2-3.4 mcg/min) at three hours, and increased by 2.7 mcg/min (95% CI 1.4-4.0 mcg/min) at six hours after vasopressin initiation. NE = norepinephrine.

e-Figure 5. Subgroup Analysis of Change in Norepinephrine-Equivalent Catecholamine Dose After Vasopressin Start by pH in Medical Intensive Care Unit Patients



Change in norepinephrine-equivalent catecholamine dose at one hour (A; n=880), three hours (B; n=875), and at six hours (C; n=874) after vasopressin start by arterial pH at vasopressin initiation in medical intensive care patients. Lines represent the predicted change in norepinephrine-equivalent catecholamine dose from a linear regression of norepinephrine-equivalent catecholamine dose on arterial pH at vasopressin initiation. For each 0.1 unit the pH was below 7.40 at vasopressin initiation, the norepinephrine-equivalent catecholamine dose increased by 1.8 mcg/min (95% CI 0.4-3.2 mcg/min) at one hour, increased by 3.4 mcg/min (95% CI 2.1-4.7 mcg/min) at three hours, and increased by 3.3 mcg/min (95% CI 1.9-4.7 mcg/min) at six hours after vasopressin initiation. NE = norepinephrine

Supplemental References

1. Kelly AM, McAlpine R, Kyle E. Venous pH can safely replace arterial pH in the initial evaluation of patients in the emergency department. *Emerg Med J.* 2001;18(5):340-342.
2. Kelly AM, Kyle E, McAlpine R. Venous pCO(2) and pH can be used to screen for significant hypercarbia in emergency patients with acute respiratory disease. *J Emerg Med.* 2002;22(1):15-19.
3. Treger R, Pirouz S, Kamangar N, Corry D. Agreement between central venous and arterial blood gas measurements in the intensive care unit. *Clin J Am Soc Nephrol.* 2010;5(3):390-394.
4. Adrogué HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. *N Engl J Med.* 1989;320(20):1312-1316.
5. Middleton P, Kelly AM, Brown J, Robertson M. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J.* 2006;23(8):622-624.
6. Goradia S, Sardaneh AA, Narayan SW, Penm J, et al: Vasopressor dose equivalence: A scoping review and suggested formula. *J Crit Care* 2021; 61:233-240.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5-6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6-7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8, 17
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8, 19

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.