

HEALTH CARE REFORM

Chronicle of an Unforetold Death

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Writing in sorrow and anger, I express up front my potential conflict of interest in interpreting the facts surrounding the death of my wife, Barbara Starfield, MD, MPH.

Within hours after her sudden and unexpected death, I notified the dean of the Johns Hopkins Bloomberg School of Public Health, on whose faculty she served, that Barbara had apparently died of a coronary occlusion. He relayed the news around the world. Devoted to improving effectiveness and equity in health care, Barbara received many tributes.¹

Because she died while swimming alone, an autopsy was required. The immediate cause of death was “pool drowning,” but the underlying condition, “cerebral hemorrhage,” stunned me. The pathologist attributed the massive hemorrhage to cerebral amyloid angiopathy (CAA), listing “anti-coagulation therapy” on the death certificate under “other significant conditions.” No significant occlusion of any of her coronary arteries was found. A scalp bruise adjacent to a larger bruise on her right temporalis muscle was observed, but no skull fractures. Patchy microhemorrhages were observed in the cerebral cortex.

*See also pages 1144
and 1145*

Cerebral amyloid angiopathy is not rare in the elderly, estimated to occur in 8.0% of those aged 75 to 84 years (Barbara's age group) and 12.1% in those aged 85 years and older.³ However, a large proportion of patients in whom CAA is diagnosed post mortem do not die of cerebral hemorrhage.³ Nonfatal microhemorrhage associated with CAA can be detected by magnetic resonance imaging.⁴

Barbara started taking low-dose aspirin after coronary insufficiency had been diagnosed 3 years before her death, and clopidogrel bisulfate (Plavix) after her right main coronary artery had been stented 6 months after the diagnosis. She reported to the cardiologist that she bruised more easily while taking clopidogrel and bled longer following minor cuts. She had no personal or family history of bleeding tendency or hypertension.

The autopsy findings and the official lack of feedback prompted me to call attention to deficiencies in medical care and clinical research in the United States (**Table 1**) reified by Barbara's death and how the deficiencies can be rectified. Ironically, Barbara had written about all of them.

LACK OF COORDINATION OF CARE

When patients die suddenly and unexpectedly and are not in a health care facility, no routine procedure is required for notifying their physicians, even if the patient is autopsied. (Unfortunately, only 8% of deaths were autopsied in the United States in 2007, and only 2% in Barbara's age group.⁵) Had I, as next of kin, not informed Barbara's physicians, they would not have learned of her death until she missed her next appointment, if then.

Barbara strongly believed that for common conditions, primary care physicians should have primary responsibility for management,⁶ coordinating care with specialists as needed. By amending the standard death certificate to include the name of the decedent's primary care physician and by requiring state departments of vi-

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tal statistics to notify the physician when the death certificate is filed, physicians will be made aware of their patients' deaths (and causes if the patient is autopsied). The primary care physician should then be responsible for notifying the specialists involved in the patient's care.

UNDERREPORTING OF ADVERSE DRUG EVENTS

In response to my request, Barbara's cardiologist submitted an adverse drug event report to the US Food and Drug Administration (FDA), stating that she was receiving anticlotting medications that might have contributed to her cerebral hemorrhage. The "report may be the critical action that prompts a modification in use or design of the product, improves the understanding of the safety profile of the drug or device and leads to increased patient safety."⁷ The FDA report form does not ask for patient identification and cannot be used for malpractice litigation.

Barbara lamented that adequate care "is not realized when likely adverse events are not systematically recorded and studied,"^{8(p65)} which is often the case.⁹ She also noted that iatrogenic causes constitute the third leading cause of death in the United States.¹⁰ Oral antiplatelet agents are the third most frequent category of drugs implicated in hospitalizations for adverse events in patients aged 65 years or older.¹¹

The FDA should inform the public that anyone can file the agency's adverse event report. Penalties (financial and criminal) should be imposed when a drug company withholds information from the FDA on aggregated adverse events of drugs that it manufactures. Postmarket surveillance of new drugs should be expanded. Barbara and I urged more stringent enforcement of the FDA's rules for postmarket surveillance.¹²

MULTIMORBIDITY

Barbara, who emphasized the importance of multimorbidity,¹³ was caught in its web: CAA, discovered post mortem, could have increased her risk of cerebral hemorrhage from head trauma, perhaps by her swim-

ming into the curved wall of the pool. Once she started to bleed, clopidogrel drug regimen could have made the bleeding worse. Patients taking clopidogrel were significantly more likely than patients taking only aspirin to experience an increase in intracerebral hematoma volume ($P = .05$) and possibly to have twice the mortality rate (8 vs 4 per 28 patients; $P = .19$).¹⁴

Greater awareness of the high frequency of CAA in those aged 65 and older might lead physicians caring for elderly patients who are taking antiplatelet drugs to be alert for transient or increasing cognitive impairment that might indicate microhemorrhages and to follow up with a thorough neurological evaluation and magnetic resonance imaging if indicated. Primary care physicians are better trained than cardiologists to be on the lookout for cognitive changes.

Multimorbidity gives reason to question, as Barbara repeatedly did, whether the emphasis on specialty care in the United States is misplaced. "Specialty care for morbidity that is not in the area of the physician's special competence," Barbara wrote, "compromises quality of care."¹³ Many of the studies on clopidogrel following coronary stent placement have been directed by cardiologists and focus on the reduction of atherothrombotic outcomes, which may be high in the short term, rather than on bleeding, which is spread throughout the duration of drug treatment.

As our population ages and morbidities accumulate, the United States needs policies that redirect American medicine to primary care physicians. By providing continuing care over time, primary care physicians can practice person-focused as opposed to disease-centered care.⁸ They can get to know their patients as persons and become aware of their multiple morbidities, alert to the presence or possibility of disease and/or drug interactions.

THE LIMITED SCOPE OF CLINICAL TRIALS

The FDA relies on randomized controlled trials (RCTs) to establish a

Table 1. Lessons From Barbara's Death

Lack of coordination—providers are not notified of sudden and unexpected deaths
Underreporting of possible adverse drug events
Multimorbidity—best appreciated by primary care physicians
Inadequacy of randomized controlled trials
Potential bias in randomized controlled trials sponsored and supported by the pharmaceutical industry

new drug's safety (harm), as well as its efficacy, in granting premarket approval. Important as they are, such trials have limitations, as Barbara pointed out.¹³ Problems of inadequate sample size, short duration, and comorbidity are exemplified by the 2 RCTs on whose findings the use of clopidogrel following the percutaneous insertion of coronary artery stents is based (**Table 2**). Both studies were of short duration, either 1 year¹⁵ or an average of 8 months¹⁶ after stenting. The statistical significance of both benefit and harm end points is shown in Table 2. Only with composite end points (eg, reduced cardiovascular death and myocardial infarction) is statistically significant benefit attained. In one of these studies,¹⁵ a borderline association of clopidogrel with harm (major bleed; $P = .07$) was observed.

Despite the short follow-up periods and the slim statistical significance, many cardiologists have prescribed clopidogrel for longer than 1 year after a stenting procedure, as in Barbara's case.

Since these studies were reported, several others have been conducted, of which 4 are shown in Table 2. Two of these were RCTs.^{17,20} The other 2 were population-based registry studies of patients being treated in practice, not in clinical trials.^{18,19} Three of the 4 had more patients than the first 2. None of these later studies found a significant benefit of clopidogrel administered for a duration of longer than 6 or 12 months following coronary artery stenting. Two showed a significant increase in major bleeds ($P = .007$ in Tsai et al¹⁸ and $P < .001$ in Valgimigli et al²⁰) and another a borderline increase.¹⁹

Table 2. Comparison of 6 Clopidogrel Studies After Coronary Artery Stenting

Source	Design	No. of Patients	Mean Duration, mo	P Value		Drug Company Sponsorship/Support
				Benefit	Harm	
CREDO ¹⁵	RCT	1818	12 ^a	.04 ^b	.07	+/+
PCI-CURE ¹⁶	RCT	2658	8 (3-12)	.047 ^c ; .03 ^d	NS	+/-
Park et al ¹⁷	RCT	2702	28-38	NS	NS	-/-
Tsai et al ¹⁸	Registry	7689	13-18	NS	.007	-/-
Sørensen et al ¹⁹	Registry	11 680	18 vs 6 ^e	NS	.06	-/-
Valgimigli et al ²⁰	RCT	2013	24 vs 6 ^e	NS	<.001	-/-

Abbreviations: CREDO, Clopidogrel for the Reduction of Events During Observation; NS, not significant; PCI-CURE, Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Events; RCT, randomized controlled trial; +, received industry sponsorship/support; -, did not receive industry sponsorship/support.

^aFrom 29 days to 1 year.

^bComposite of death, myocardial infarction, and stroke.

^cComposite of cardiovascular death and myocardial infarction.

^dComposite of cardiovascular death, myocardial infarction, and any revascularization.

^eMonths taking clopidogrel.

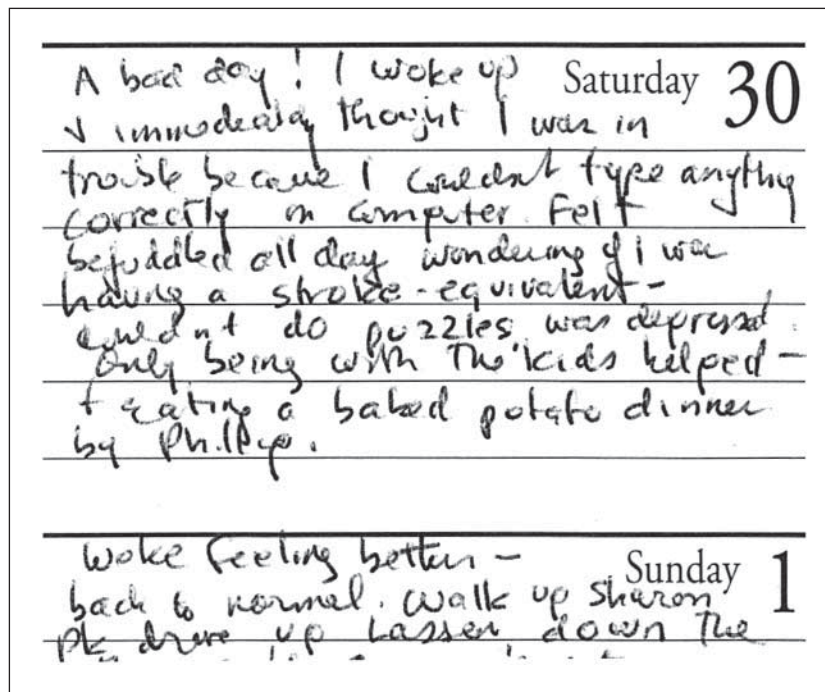


Figure. A page from Barbara Starfield's calendar diary written 6 weeks before her death.

Barbara reported minor bleeding to her cardiologist following percutaneous stent insertion. Minor bleeding was observed in 3.5% of patients taking clopidogrel in one of the early RCTs, significantly more than in the group receiving only aspirin ($P = .03$).¹⁶ To my knowledge, no study has examined whether patients experiencing minor bleeding who continue taking clopidogrel are more likely to sustain a major bleed.

All but one of the later studies in Table 2 were published before Barbara died. It is puzzling that their negative findings on clopidogrel did not reach many practicing cardiolo-

gists. Neither the American Heart Association nor the FDA issued an alert on prolonged use of the drug. The newsletter *Worst Pills, Best Pills* told readers that “long-term clopidogrel may be no better than aspirin” and warned of its bleeding potential.^{21(p5)} That newsletter, which should be read by more physicians, enables patients to question their physicians about the safety of the drugs they are taking. Barbara read the newsletter, but this issue was published after she died.

When a specific adverse event is expected (eg, bleeding with clopidogrel), adverse event reporting to FDA should be mandatory, and the

manufacturer should be obliged to conduct postmarket surveillance. When a harmful effect is confirmed, the FDA should issue a warning to physicians and require a warning in the package insert. Risks should be weighed against benefits to decide whether the drug should be removed from the market.

POTENTIAL BIAS IN RCTS SPONSORED AND SUPPORTED BY THE PHARMACEUTICAL INDUSTRY

Both of the early RCTs that reported a benefit of clopidogrel after stenting were sponsored by the drug's original manufacturers.^{15,16} The title of one of these studies¹⁶ is misleading, maintaining that the study was “long-term” although the average follow-up was only 8 months. In the other of these RCTs, “medical specialists employed by the sponsors provided scientific input into the study design,” and at least 2 investigators either received support from or consulted for the manufacturer.^{15(p2419)} Neither of the RCTs that failed to show a benefit of long-term clopidogrel use,^{17,20} nor the reports using registry data with a similar negative finding,^{18,19} received industry support. In a 2008 review,^{22(p109)} pharmaceutical company sponsorship of clinical trials was strongly associated with results “that favor the sponsors' interests.”

Declaring that a conflict of interest exists does not ensure that a study is well designed, executed, and interpreted. Before scientific journals

consider an RCT for publication, they should require a declaration that “The funders have no role in study design, study conduct, data management, and interpretation”^{23(p11)} and do not provide direct support to any researcher engaged in the research.

CONCLUDING COMMENTS

Could Barbara’s death have been foretold? On a Saturday 6 weeks before her death, Barbara wondered whether she was having a “stroke equivalent” (**Figure**). The next day she wrote “feeling better” and took a strenuous walk. She did not report this episode to her primary care physician or cardiologist, neither of whom was routinely available on weekends. Had the symptoms of the stroke equivalent continued throughout the weekend, or had they occurred on another weekday, Barbara *might* have consulted her primary care physician. And *if* her primary care physician referred her for an magnetic resonance imaging, and *if* the magnetic resonance imaging revealed microhemorrhage, she *might* have discontinued clopidogrel treatment in consultation with her cardiologist. Whether this would have prolonged Barbara’s life, or for how long, is impossible to say.

“When people pass away,” Murakami²⁴ asks, “do their thoughts just vanish?” Barbara’s thoughts as she transitioned from life to death will never be known, but her thoughts while she lived will not just vanish. They are already part of the thinking of many medical researchers and practitioners around the world and have had a profound effect on health care policies in many countries, least of all her own.

Specialization, fragmentation, drug-orientation, and profit-seeking help make American medical care the most expensive in the world, but not the safest or most effective. The lessons from Barbara’s death should be put in the perspective of the millions who cannot af-

ford even basic services in our expensive system and suffer as a result.

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REFERENCES

1. Watts G. Obituary: Barbara Starfield. *Lancet*. 2011; 378:564.
2. Barbara Starfield memorial page. Johns Hopkins Bloomberg School of Public Health, Department of Health Policy and Management website. www.jhsph.edu/dept/hpm/starfield_memorial.html. Accessed May 1, 2012.
3. Biffi A, Greenberg SM. Cerebral amyloid angiopathy: a systematic review. *J Clin Neurol*. 2011; 7(1):1-9.
4. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. *Stroke*. 2004;35(6):1415-1420.
5. Hoyert DL. The changing profile of autopsied deaths in the United States, 1972-2007. *NCHS Data Brief*. 2011;(67):1-8.
6. Starfield B, Shi L, Macincio J. Contribution of primary care to health systems and health. *Milbank Q*. 2005;83(3):457-502.
7. HIPAA compliance for reporters to FDA MedWatch. US Food and Drug Administration website. www.fda.gov/Safety/MedWatch/HowToReport/ucm085589.htm. Accessed May 1, 2012.
8. Starfield B. Is patient-centered care the same as person-focused care? *Perm J*. 2011;15(2):63-69.
9. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2009;32(1):19-31.
10. Starfield B. Is US health really the best in the world? *JAMA*. 2000;284(4):483-485.
11. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011; 365(21):2002-2012.
12. Holtzman NA, Starfield B. Withdrawing FDA approval of midodrine after marketing. *JAMA*. 2011; 305(8):781-782.
13. Starfield B. Threads and yarns: weaving the tapestry of comorbidity. *Ann Fam Med*. 2006;4(2):101-103.
14. Campbell PG, Yadla S, Sen AN, Jallo J, Jabbour P. Emergency reversal of clopidogrel in the setting of spontaneous intracerebral hemorrhage. *World Neurosurg*. 2011;76(1-2):100-104, discussion 59-60.
15. Steinhubl SR, Berger PB, Mann JT III, et al; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288(19):2411-2420.
16. Mehta SR, Yusuf S, Peters RJ, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-533.
17. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med*. 2010;362(15):1374-1382.
18. Tsai TT, Ho PM, Xu S, et al. Increased risk of bleeding in patients on clopidogrel therapy after drug-eluting stents implantation: insights from the HMO Research Network-Stent Registry (HMORN-stent). *Circ Cardiovasc Interv*. 2010;3(3):230-235.
19. Sorensen R, Abildstrom SZ, Weeke P, et al. Duration of clopidogrel treatment and risk of mortality and recurrent myocardial infarction among 11 680 patients with myocardial infarction treated with percutaneous coronary intervention: a cohort study. *BMC Cardiovasc Disord*. 2010;10:6.
20. Valgimigli M, Campo G, Monti M, et al; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short-versus long-term duration of dual antiplatelet therapy after coronary stenting: a randomized multicentre trial [published online ahead of print March 21, 2012]. *Circulation*. 2012;125(16):2015-2026 doi:10.1161/CIRCULATIONAHA.111.071589.
21. Anonymous. Inadvertent adverse reactions with commonly used drugs. *Worst Pills, Best Pills News*. 2012;18:1-6.
22. Sismondo S. Pharmaceutical company funding and its consequences: a qualitative systematic review. *Contemp Clin Trials*. 2008;29(2):109-113.
23. Collet JP, Cayla G, Cuisset T, et al. Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. *Am Heart J*. 2011;161(1): 5-12.e5. doi:10.1016/j.ahj.2010.09.029.
24. Murakami H. *What I Talk About When I Talk About Running*. New York, NY: Vintage International; 2009:76.