contains a broad spectrum of lipid-rich lipoprotein particles, abundant lipid carrier proteins, and a host of other factors that all could potentially negate the reported effects on EPCR. Thus, the implications of EPCR lipid editing, EPCR encryption, and cellular APC resistance for vascular disease remain to be determined. Notwithstanding, $sPLA_2$s are expressed abundantly in atherosclerotic lesions and a variety of inflammatory conditions. In addition, the link between plasma levels of $sPLA_2$ and cardiovascular disease seems consistent with a potential role of $sPLA_2$s in inducing EPCR lipid modifications and possible contributions thereof to cardiovascular disease.[8,10] Should such links become more tangible then evaluation of $sPLA_2$ inhibitors as a therapeutic strategy to boost the endogenous protein C anticoagulant and cytoprotective pathways might become worthwhile.[10]

As is often the case with new discoveries that push the frontiers of our knowledge, they raise more questions than they answer. Certainly, the tantalizing observations by López-Sagaseta and colleagues raise many new questions, but most importantly, they stimulate the conceptualization of new basic research with the potential of translation into novel therapeutic approaches to combat thrombosis and vascular diseases.

Conflict-of-interest disclosure. The authors declare no competing financial interests. ■

REFERENCES

1. Lopez-Sagaseta J, Puy C, Tamayo I, et al. sPLA2-V inhibits EPCR anticoagulant and antiapoptotic properties by accommodating lysophosphatidylcholine or PAF in the hydrophobic groove. *Blood*. 2012;119(12):2914-2921.
2. Fukudome K, Esmon CT. Identification, cloning, and regulation of a novel endothelial cell protein C/activated protein C receptor. *J Biol Chem*. 1994;269(42):26486-26491.
3. Mosnier LO, Zlokovic BV, Griffin JH. The cytoprotective protein C pathway. *Blood*. 2007;109(8):3161-3172.
4. Castoldi E, Rosing J. APC resistance: biological basis and acquired influences. *J Thromb Haemost*. 2010;8(3):445-453.
5. Oganesyan V, Oganesyan N, Terzyan S, et al. The crystal structure of the endothelial protein C receptor and a bound phospholipid. *J Biol Chem*. 2002;277(28):24851-24854.
6. Barral DC, Brenner MB. CD1 antigen presentation: how it works. *Nat Rev Immunol*. 2007;7(12):929-941.
7. Venkataswamy MM, Porcelli SA. Lipid and glycolipid antigens of CD1d-restricted natural killer T cells. *Semin Immunol*. 2010;22(2):68-78.
8. Mallat Z, Lambeau G, Tedgui A. Lipoprotein-associated and secreted phospholipases A in cardiovascular disease: roles as biological effectors and biomarkers. *Circulation*. 2010;122(21):2183-2200.
9. Esmon CT. The endothelial protein C receptor. *Curr Opin Hematol*. 2006;13(5):382-385.
10. Suckling K. Phospholipase A2s: developing drug targets for atherosclerosis. *Atherosclerosis*. 2010;212(2):357-366.

● ● ● TRANSPLANTATION

Comment on Styczynski et al, page 2935

A donor's a person, no matter how small

Michael A. Pulsipher UNIVERSITY OF UTAH SCHOOL OF MEDICINE

After 30+ years of considering BM donation from sibling children a safe and effective standard based on 2 single-center studies,[1,2] Styczynski and colleagues in this edition of *Blood* provide us with a multicenter, prospective study of safety outcomes of 453 pediatric BM and PBSC donors.[3]

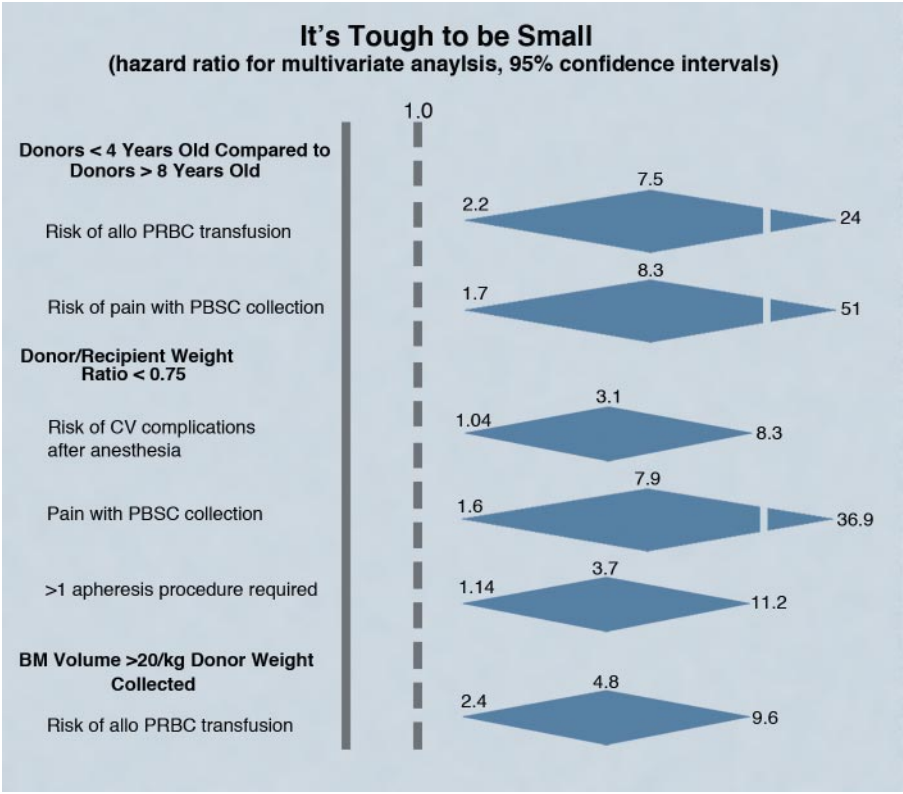
The work is long overdue. In the midst of our focus on improving outcomes of their sicker siblings, we have too-long neglected what should be an ongoing task of ensuring that we (1) know in detail current common and rare risks of these procedures and (2) work to minimize or eliminate side-effects in these healthy children as they go through the BM or peripheral blood stem cell (PBSC) collection process.

This study confirms our long-held belief that BM and PBSC collection from minor donors is generally safe, resulting in temporary discomfort in a portion of donors (only 1 severe adverse event [nonlife-threatening] was reported in 453 donations). This distinguishes BM and PBSC donation from riskier sibling solid organ donation, counter to a recent American Academy of Pediatrics policy statement that calls for BM/PBSC and solid organ donors to be approached in a similar fashion.[4] But the data presented in the study points out an area where we have room for improvement. It is clear that centers vary tremendously in the way they practice, with consequences for the donor. This gives us an opportunity to define best practices and raise the safety bar even further.

The most obvious lesson we learn from this study is that both being small and being much smaller than your recipient puts donors at higher risk for requiring a blood transfusion and additional apheresis procedures, pain, and cardiovascular complications after anesthesia (see figure). Stycsynski et al clearly point out that removing > 20 cc/kg of marrow from donors markedly increases their likelihood of needing an allogeneic packed red blood cell (PRBC) transfusion (hazard ratio 4.8, $P < .001$). Harvesting a maximum of 20 cc/kg from a donor is already the standard of care in most North American centers, and if this approach is followed, transfusions of allo-PRBCs to donors can largely be avoided. But the study brings to the fore a dilemma often encountered in pediatric BMT—what do you do when the sibling donor is much smaller than the recipient? The highest-risk donors were < 4 years old, and most of these donors were smaller than their recipients. Harvesting a maximum of 20 cc/kg from a donor means that if their recipient is twice their weight (average 2-year-old donating to a 7-year-old) one will be giving 10 cc/kg to the recipient, an amount considered reasonable only if red cell depletion for ABO mismatch is not required. It is clear that too few cells to a recipient leads to worse outcomes, so when larger differences in weight occur or when red cell depletion is needed, harvesting more than 20 cc/kg may be needed.

What does one do for such a donor/recipient weight discrepancy? Clearly, PBSC donation has been shown by Styczynski and colleagues and others[5] to be safe in children and it allows multiple collections to be performed until adequate numbers of cells are collected; however, theoretical concerns regarding G-CSF administration to children linger (in spite of many reassuring articles[6]). Younger children would need apheresis catheter placement with its attendant risks, and the smallest (< 20 kg) may be exposed to PRBCs to prime an apheresis machine, defeating the purpose. In addition, current literature suggests that the risks of chronic GVHD in children receiving PBSCs may outweigh their benefit, although this has not been studied versus the competing risk of low cell dose.

Another approach to the problem would be storing autologous units from children when exceeding 20 cc/kg from a harvest is anticipated. This takes preparation, however, and



Risk of selected adverse events in small children after BM or PBSC harvest for their siblings.

would only be a reasonable solution if obtaining the higher volume did not change the quality of the product. Another possibility, G-CSF–primed BM harvest, has been shown to at least double $CD34^+$ yield/cc, but only moderately sized studies have been performed using this approach.[7] A final possible solution would be to consider an unrelated donor, but matched related sibling donor transplantation consistently yields less GVHD and similar or better survival in children compared with the use of matched unrelated donors.[8] Studies are needed to address this perplexing issue, but allowing allo-PRBC transfusions to be performed in healthy pediatric BM donors when they can be prevented is unacceptable, and harvesting no more than 20 cc/kg from a pediatric donor is an appropriate and reasonable safety standard.

The article by Styczynski et al is not without weaknesses. Some of the tools used to measure outcomes (eg, pain) could have been more descriptive, and there were not standardized assessments of the psychosocial status of the donors before and after the procedure (an important issue when a young child donates to a sibling who may not live). Over the past decade, the National Marrow Donor Program has validated highly descriptive tools for following donors using standardized common terminology criteria–based measures,[9] allowing a much more thorough understanding of what donors experience. In addition, well-validated methods of measuring key psychological outcomes in unrelated BM and PBSC donors have been published.[10] These tools are currently being used in a multicenter study of related donor safety (RDSafe) in North America funded by the National Heart, Lung, and Blood Institute and run through the National Marrow Donor Program/Center for International Blood and Marrow Transplant Research. Pediatric donors are a major cohort in that study, and when the study is completed, it will add even more granularity to our picture of what our child BM and PBSC donors are experiencing as they generously assist their siblings.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Buckner CD, Clift RA, Sanders JE, et al. Marrow harvesting from normal donors. *Blood*. 1984;64(3):630-634.
2. Sanders J, Buckner CD, Bensinger WI, et al. Experience with marrow harvesting from donors less than two years of age. *Bone Marrow Transplant*. 1987;2(1):45-50.
3. Styczynski J, Balduzzi A, Gil L, et al. Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective European Group for Blood and Marrow Transplantation Pediatric Diseases Working Party study. *Blood*. 2012;119(12):2935-2942.
4. Children as hematopoietic stem cell donors. *Pediatrics*. 2010;125(2):392-404.
5. Pulsipher MA, Levine JE, Hayashi RJ, et al. Safety and efficacy of allogeneic PBSC collection in normal pediatric donors: the pediatric blood and marrow transplant consortium experience (PBMTC) 1996-2003. *Bone Marrow Transplant*. 2005;35(4):361-367.
6. Pulsipher MA, Nagler A, Iannone R, et al. Weighing the risks of G-CSF administration, leukopheresis, and standard marrow harvest: ethical and safety considerations for normal pediatric hematopoietic cell donors. *Pediatr Blood Cancer*. 2006;46(4):422-433.
7. Frangoul H, Nemecek ER, Billheimer D, et al. A prospective study of G-CSF primed bone marrow as a stem-cell source for allogeneic bone marrow transplantation in children: a Pediatric Blood and Marrow Transplant Consortium (PBMTC) study. *Blood*. 2007;110(13):4584-4587.
8. Shaw PJ, Kan F, Woo Ahn K, et al. Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors. *Blood*. 2010;116(19):4007-4015.
9. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2009;113(15):3604-3611.
10. Switzer GE, Myaskovsky L, Goycoolea JM, et al. Factors associated with ambivalence about bone marrow donation among newly recruited unrelated potential donors. *Transplantation*. 2003;75(9):1517-1523.