AUTHOR QUERY FORM

LIPPINCOTT
WILLIAMS AND WILKINS

JOURNAL NAME: MPH
ARTICLE NO: 201567
QUERIES AND / OR REMARKS

QUERY NO.	Details Required	Author's Response
Q1	Please confirm whether the suggested short running title "Recurrent Arterial Thrombosis" for the article is okay. If not, please suggest an appropriate short running title not exceeding 50 characters.	
Q2	Please provide the expansion for "PE."	
Q3	Please provide the expansion for "LDL."	
Q4	Please provide the expansion for HDL."	

Recurrent Arterial Thrombosis Associated With the Antithrombin Basel Variant and Elevated Lipoprotein(a) Plasma Level in an Adolescent Patient

Szabolcs Szilágyi, MD, PhD, Andrea Péter, MD,* Mária Tünde Magyar, MD, PhD,† Sándor Balogh, MD, PhD,‡ and Zsuzsanna Bereczky, MD, PhD§*

Summary: Both myocardial infarction and ischemic stroke are rare in the young. Yet a 15-year-old male patient suffered a myocardial infarction and later an ischemic stroke despite uninterrupted antiplatelet therapy. His medical history involved the surgical correction of an incomplete atrioventricular canal defect at the age of 13 years. No cardiovascular risk factors other than elevated lipoprotein(a) level could be identified. His antithrombin (AT) activity was decreased and DNA sequence analysis revealed heterozygosity for AT Basel (p.Pro41Leu), a variant with impaired heparin binding. This report supports a possible additional pathophysiological role for AT Basel and elevated lipoprotein(a) level in arterial thrombogenesis.

Key Words: arterial thrombosis, antithrombin Basel, lipoprotein(a), myocardial infarction, ischemic stroke

(*J Pediatr Hematol Oncol* 2011;00:000–000)

Myocardial infarction (MI) and ischemic stroke (IS) are both rare conditions in adolescence with different risk factors, presentation, and prognosis from those in the adult.[1,2] Premature arterial events in the young are frequently associated with the presence of congenital vascular anomalies, cardiac malformations, presence of severe inherited atherosclerotic risk factors, infective or autoimmune inflammatory diseases, and rheological disorders, whereas traditional atherosclerotic risk factors (hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking) are uncommon.[2,3]

Antithrombin (AT)—in earlier times termed AT III—is a major inhibitor of thrombin and activated factor X.[4] In the presence of heparin, the inhibition is approximately 1000-fold more effective. The prevalence of AT deficiency in the general population and in patients with venous thromboembolism (VTE) is estimated to range from 1:2000 to 1:3000 and from 1:20 to 1:200, respectively. Accordingly, patients with AT deficiency hold an approximately 25 to 50-fold relative risk for VTE.[5] In comparison, association of arterial thromboembolism with AT deficiency is extremely rare, thus no such epidemiological data is yet available. Two types of AT deficiency can be differentiated, type I deficiency means reduced level of a functionally normal molecule whereas type II deficiency represents a dysfunctional molecule. Among type II deficient cases 3 subtypes can be distinguished, the defect may involve the reactive site (type II RS), the heparin-binding site (type II HBS), or both (type II PE). The pathologic role of AT deficiency in the development of VTE is well established. In contrast, as for arterial thromboembolism the association is still ambiguous.[6] Although reports on acute arterial events associated with AT deficiency are sparsely published,[7–9] a recent epidemiologic study supported the role for AT Cambridge II, an AT type II RS variant (p.Ala384Ser) in arterial thrombosis.[10] AT Basel described in 1986 is an AT type II HBS variant with normal RS but impaired heparin binding affinity as a result of the substitution of proline by leucine at position 41.[11]

Lipoprotein(a) [Lp(a)], a cholesterol-rich plasma lipoprotein promotes both arteriosclerosis and thrombogenesis. High Lp(a) level is now considered as an independent risk factor for cardiovascular diseases (CVDs).[12] In a recent meta-analysis risk ratios for nonfatal MI and IS per 3.5-fold higher baseline Lp(a) level after adjustment for cardiovascular risk factors were 1.12 (95% confidence interval, 1.07-1.18) and 1.10 (95% confidence interval, 1.02-1.18), respectively.[13]

This report supports pathophysiologic roles for AT Basel and elevated Lp(a) level in arterial thrombogenesis with a possible additional effect on the development of MI and IS in our adolescent patient.

CASE REPORT

A 15-year-old white boy was admitted to hospital complaining of sudden onset of chest pain after mild physical exercise. Diagnosed with incomplete atrioventricular septal defect in infancy he underwent surgical repair (atrial septal defect and cleft mitral valve closure) at the age of 13 years. Elevated cardiac troponin I and total and cardiac specific creatine kinase levels suggested myocardial damage localized to the anterior wall of the left ventricle by echocardiography scan and 12-lead ECG (Fig. 1). Coronary angiogram indicated overall angiographically normal coronary arteries and revealed a sole thrombotic occlusion of the left anterior descending coronary artery. The vessel was successfully recanalized by intracoronary stent implantation (Fig. 2). Moderate leukocytosis on admission was caused by elevated absolute neutrophil count; however, neither clinical symptoms nor further laboratory investigations were indicative of inflammatory process.

Twenty months later, the patient suffered IS associated with left-sided hemiparesis despite continuously having been on effective

Received for publication April 9, 2011; accepted August 16, 2011.
From the *Institute of Cardiology; †Department of Neurology; §Clinical Research Center, Thrombosis and Haemostasis Research Group of the Hungarian Academy of Sciences, University of Debrecen, Medical and Health Science Center, Debrecen; and ‡National Institute for Primary Health Care, Budapest, Hungary.
Szabolcs Szilágyi and Andrea Péter have contributed equally to this work.
The authors declare no conflict of interest.
Reprints: Szabolcs Szilágyi, MD, PhD, Institute of Cardiology, University of Debrecen, Medical and Health Science Center, Móricz Zs. krt. 22., 4032 Debrecen, Hungary (e-mail: szabszil@-dote.hu).

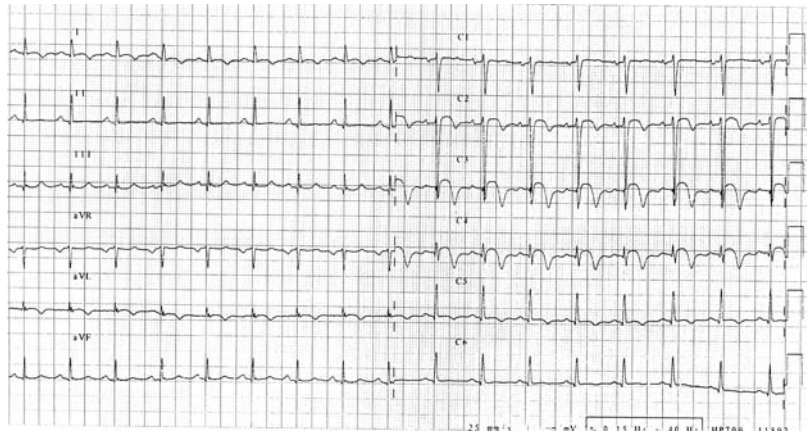

FIGURE 1. Electrocardiogram on admission to coronary angiography showing ST-segment elevation on leads I, aVL, and V2 to V4 with T-wave inversion on leads I, aVL, and V2 to V5.

antiplatelet therapy confirmed by PFA-100 Closure Time Determination, Platelet Aggregation, and Secretion Studies and investigation of vasodilator-stimulated phosphoprotein phosphorylation by flow cytometry (Coll/EPI closure time: > 300 s—reference range: 63 to142 s; ADP aggregation—5 μM, 20 μM, and 40 μM in the presence of PGE1: significantly decreased, single-phase aggregation, no ATP secretion; platelet reactivity index: 39.8%—control: 77.3%, respectively). Computed tomography angiography showed partial occlusion at the bifurcation of the right middle cerebral artery. Successful systemic thrombolysis allowed full neurological recovery; however, ischemic cerebral lesion remained (Fig. 3). Transthoracic and transesophageal echocardiography scans conducted by an experienced examiner could not detect any cardiac source for arterial embolism. Receiving combined antiplatelet and oral anticoagulation therapy the patient remains free of symptoms to this day.

Cardiovascular risk factors and family history for CVDs were thoroughly investigated after the MI (Table 1). The majority of the laboratory test values were within their reference range with the exception of an elevated Lp(a) level. Furthermore, AT activity was decreased, whereas the AT antigen level was normal suggesting a type II AT deficiency. To reveal a possible genetic background for decreased AT activity direct DNA sequencing of the coding regions including exon-intron boundaries and promoter region of the AT gene was performed. A cytosine to thymine nucleotide base change

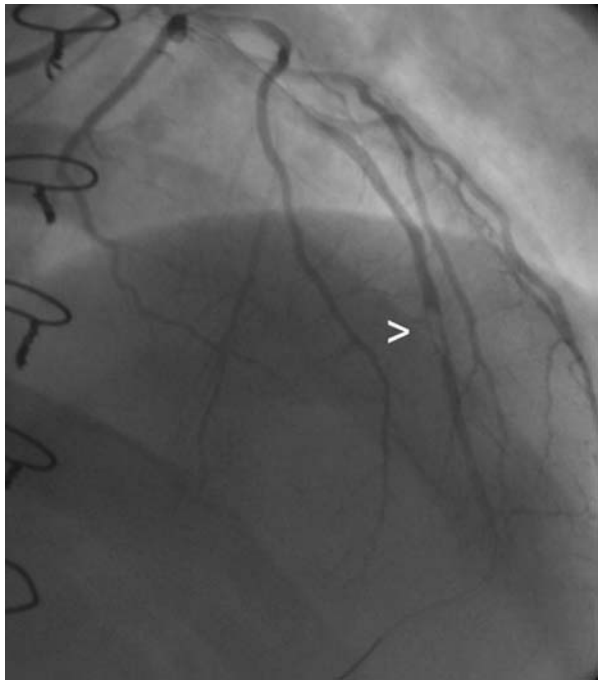

FIGURE 2. Coronary angiogram characteristic for intravascular thrombus (arrowhead) in the middle segment of the left anterior descending coronary artery.

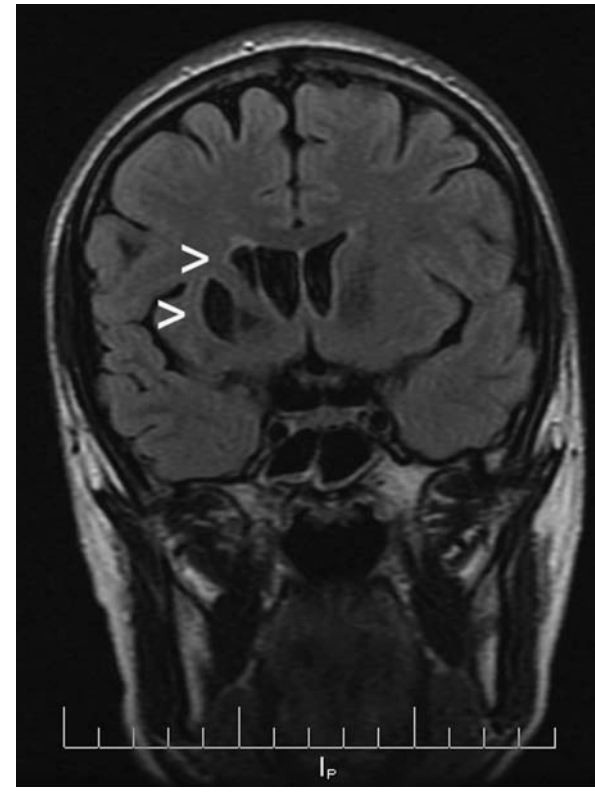

FIGURE 3. Magnetic resonance image confirming chronic ischemic lesions of the caudate and lentiform nuclei in the right hemisphere (arrowheads).

TABLE 1. Summarized Results of the Investigations for Risk Factors of Arteriosclerosis and Thrombophilia in our 15-year-old Male Patient

Data Based on Clinical Investigations and Interview	Method	Interpretation
Family history for CVDs	Interview	Negative
Blood pressure	Riva-Rocci, ABPM	Normal
Tests for obesity	BMI, WC	Normal
Physical activity	Interview	Normal
Alcohol abuse	Interview	No abuse
Substance abuse	Interview	No abuse
Smoking habit	Interview	Nonsmoker
Carotid artery stenosis	CDI	Negative
Recent chest trauma	Interview, CXR	Not demonstrated
Data Based on Laboratory Investigations	**Result**	**Reference Range or Cutoff Value**
Tests for diabetes mellitus		
FG (mmol/L)	4.2	3.6-6.0
HbA1c (%)	5.0	4.2-6.1
Tests for dyslipidemia		
T-CHOL (mmol/L)	3.8	< 5.2
HDL-C (mmol/L)	1.6	> 0.9
LDL-C (mmol/L)	1.6	< 3.4
TG (mmol/L)	1.3	< 1.7
Lipoprotein(a) (mg/L)	887	< 300
Tests for liver function		
ALB (g/L)	51	30-60
AST (U/L)	35	< 40
ALT (U/L)	16	< 40
TBIL (μmol/L)	23	3-17
Tests for kidney function		
CREAT (μmol/L)	68	62-106
GFR (mL/min/1.73 m^2)	> 90	> 90
Hematocrit	0.47	0.39-0.50
Platelet count (G/L)	191	150-400
White blood cell count (G/L)	15.1	4.8-10.8
C-reactive protein (mg/L)	1.6	< 5.2
Total homocysteine (μmol/L)	5.2	< 12.5
Vitamin B_{12} (pmol/L)	590	145-637
Folic acid (nmol/L)	29.7	7.0-39.7
Investigations for thrombophilia		
Fibrinogen level (g/L)	3.0	1.5-4.0
Factor VIII activity (%)	79	60-150
Antithrombin antigen (g/L)	0.27	0.19-0.31
Antithrombin activity (%)	72	80-120
Presence of lupus anticoagulant or elevated levels of anticardiolipin antibodies	Excluded	n.a.
Factor V Leiden mutation	Wild type	n.a.
MTHFR C667T mutation	Wild type	n.a.
Prothrombin 20210 A allele	Wild type	n.a.
Protein C activity (%)	128	70-130
Protein S activity (%)	76	65-140

ABPM indicates ambulatory blood pressure monitoring; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CDI, carotid duplex imaging; CREAT, creatinine; CVDs, cardiovascular diseases; CXR, chest x-ray; FG, fasting glucose; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; MTHFR, methylenetetrahydrofolate reductase; n.a., not available; TBIL, total bilirubin; T-CHOL, total cholesterol; TG, triglyceride; WC, waist circumference.

within the codon 210 and a consequent proline to leucine substitution at position 41 in the amino acid sequence were identified in heterozygous form (AT Basel).

DISCUSSION

Imaging techniques demonstrated intra-arterial thrombi and normal vascular anatomy with no signs of undue atherosclerosis or inflammatory disease in both the coronary and the cerebral arteries. Hence, a hypercoagulable state rather than structural damage or vasoactive mechanism could be suggested for the cause of the recurrent arterial occlusion.

Hemostasis laboratory investigations excluded the presence of most common hypercoagulable conditions, but revealed type II AT deficiency caused by a single amino acid exchange (p.Pro41Leu, AT Basel) in the N-terminal region of the protein. This mutation leads to impaired heparin cofactor activity of AT—a type II HBS variant.[11] Most of the mutations modifying the heparin binding affinity of AT published so far are located in the N-terminal region of the molecule and are generally associated with lower thrombosis risk compared with other types of AT deficiency.[14] Although most of the patients with such mutations suffered from venous thrombosis severe arterial thrombosis was also described in the case of homozygous HBS mutation.[15] According to our knowledge, this is the first case to report AT Basel associated with arterial thrombosis.

Lp(a) consists of a cholesterol-rich LDL-like particle and a plasminogen-like glycoprotein, apolipoprotein(a). Although the physiological function of Lp(a) is still unclear in consequence of its dual structure, Lp(a) is implicated in the process of both atherosclerosis (eg, by promoting plaque inflammation and increasing vascular smooth muscle cell proliferation) and thrombosis (by a combined prothrombotic and antifibrinolytic effect).[16] It is to note, however, that despite its presumptive association with arterial thromboembolism the role of Lp(a) in the development of venous thromboembolic events is still controversial.[17,18] On the basis of recent meta-analyses high Lp(a) plasma level is now considered to be an independent cardiovascular risk factor, that is, Lp(a)-associated risk does not depend on increased non-HDL cholesterol concentrations nor on the levels or presence of other risk factors.[12] Increased Lp(a) level is determined mainly genetically, thus its robust and specific association with CVD in adults presumes that Lp(a) is also causally related to CVD in the young.[19] The implication of Lp(a) in both premature MI and childhood IS is therefore suggested.[2,20]

In the case of AT deficiencies, similarly to other thrombophilias, a decision on long-term therapy should be made knowing the circumstances of the thrombotic event and weighing up all the patient's risk factors for recurrence. After VTE, long-term vitamin K antagonist therapy should be initiated. Nevertheless, long-term antithrombotic treatment after an arterial thrombotic event is less definite. In the presence of overt arteriosclerosis or its risk factors, antiplatelet therapy is thought to be sufficient. In contrast, if AT deficiency is deemed to be one of the main reasons for the thrombotic event long-term anticoagulation, an approach based on theoretical considerations rather than solid evidence, may be appropriate.[4] The failure of lone antiplatelet therapy to prevent a second arterial thrombosis in our young patient with an AT type II HBS variant supports this assumption.

Elevated Lp(a) as an independent genetic risk factor should be considered in the clinical management of intermediate or high-risk cardiovascular patients. The scope of therapeutic interventions available for lowering Lp(a)

plasma level is unfortunately rather limited. It is generally not influenced by lifestyle modification. Aspirin was shown to be useful; the effect of statins and fibrates on Lp(a) level was modest and highly variable, whereas anabolic steroids and estrogens are not suitable for long-term therapy. At present, despite its still ambiguous mechanism of action niacin—nicotinic acid—is the only drug with well established Lp(a) lowering effect. The dose-dependent reduction of Lp(a) level by up to 30% to 40% is accompanied by advantageous impact on the overall lipid profile. The widespread application of niacin is, however, set back by its gastrointestinal and cutaneous side effects and the interindividual differences in efficacy.[16] Yet, in case of intermediate or high absolute risk for CVD, therapeutic recommendation suggests lowering of Lp(a) to a desirable level below the 80th percentile (< 500 mg/L).[19] Hence, in patients with premature or recurrent CVD and increased Lp(a) level, in addition to the effective cholesterol reduction with a statin, the introduction of niacin in the therapy may be justified.

Reports on the association of AT type II HBS mutations with arterial thrombosis are rare. Here, the presumably additional effect of the high Lp(a) level on the prothrombotic condition caused by impaired AT activity could have contributed to the development of recurrent arterial thrombosis. We conclude that in young patients presenting with arterial thrombotic event but no predisposing medical history or conspicuous risk factors prudent investigation for special conditions such as thrombophilia or recently established cardiovascular risk factors—for example, Lp(a)—should be conducted. In addition, if an AT type II HBS variant is identified in the background of the thrombotic event introduction of oral anticoagulant therapy is recommended regardless of its arterial or venous nature.

ACKNOWLEDGMENT

The authors express their gratitude to Prof. István Édes for helpful comments on the article.

REFERENCES

1. Mahle WT, Campbell RM, Favaloro-Sabatier J. Myocardial infarction in adolescents. *J Pediatr*. 2007;151:150–154.
2. Bernard TJ, Manco-Johnson MJ, Goldenberg NA. The roles of anatomic factors, thrombophilia, and antithrombotic therapies in childhood-onset arterial ischemic stroke. *Thromb Res*. 2011;127:6–12.
3. Vivo RP, Krim SR. ST elevation myocardial infarction in a teenager: case report and review of the literature. *South Med J*. 2009;102:523–526.
4. Patnaik MM, Moll S. Inherited antithrombin deficiency: a review. *Haemophilia*. 2008;14:1229–1239.
5. Muszbek L, Bereczky Z, Kovács B, et al. Antithrombin deficiency and its laboratory diagnosis. *Clin Chem Lab Med*. 2010;48(suppl 1):S67–S78.
6. Boekholdt SM, Kramer MH. Arterial thrombosis and the role of thrombophilia. *Semin Thromb Hemost*. 2007;33:588–596.
7. Calcaterra D, Martin JT, Ferneini AM, et al. Acute mesenteric and aortic thrombosis associated with antithrombin deficiency: a rare occurrence. *Ann Vasc Surg*. 2010;24:415.e5–415.e7.
8. Peovska I, Maksimovic J, Kalpak O, et al. Recurrent myocardial infarction in a young football player with antithrombin III deficiency. *Cardiol J*. 2008;15:463–466.
9. Tu CM, Hsueg CH, Chu KM, et al. Simultaneous thromboses of double coronary arteries in a young male with antithrombin III deficiency. *Am J Emerg Med*. 2009;27:1169.e3–1169.e6.
10. Roldan V, Ordonez A, Marin F, et al. Antithrombin Cambridge II (A384S) supports a role for antithrombin deficiency in arterial thrombosis. *Thromb Haemost*. 2009;101:483–486.
11. Chang JY, Tran TH. Antithrombin III Basel: identification of a Pro-Leu substitution in a hereditary abnormal antithrombin with impaired heparin cofactor activity. *J Biol Chem*. 1986; 261:1174–1176.
12. Kamstrup PR, Benn M, Tybjaerg-Hansen A, et al. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. 2008;117:176–184.
13. Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412–423.
14. Aiach M, Gandrille S, Emmerich J. A review of mutations causing deficiencies of antithrombin, protein C and protein S. *Thromb Haemost*. 1995;74:81–89.
15. Chowdhury V, Lane DA, Mille B, et al. Homozygous antithrombin deficiency: report of two new cases (99 Leu to Phe) associated with arterial and venous thrombosis. *Thromb Haemost*. 1994;72:198–202.
16. Kamstrup PR. Lipoprotein(a) and ischemic heart diseasea causal association? A review. *Atherosclerosis*. 2010;211: 15–23.
17. Salobir B, Sabovic M, Peternel P, et al. Fibrinolytic parameters and lipoprotein(a) in young women with myocardial infarction. *Angiology*. 2002;53:157–163.
18. Vormittag R, Vukovich T, Stain M, et al. Lipoprotein (a) in patients with spontaneous venous thromboembolism. *Thromb Res*. 2007;120:15–20.
19. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31:2844–2853.
20. Zorio E, Falco C, Arnau MA, et al. Lipoprotein (a) in young individuals as a marker of the presence of ischemic heart disease and the severity of coronary lesions. *Haematologica*. 2006;91:562–565.

Author Reprints

For *Rapid Ordering* go to: www.lww.com/periodicals/author-reprints

Journal of Pediatric Hematology & Oncology

Lippincott Williams & Wilkins
a Wolters Kluwer business

Order

Author(s) Name

Title of Article

*Article # *Publication Mo/Yr

**Fields may be left blank if order is placed before article number and publication month are assigned.*

Quantity of Reprints ____ $_____

Covers (Optional) _____ $_____

Shipping Cost $_____

Reprint Color Cost $_____

Tax $_____

Total $_____

REPRINTS ORDERED & PURCHASED UNDER THE AUTHOR REPRINTS PROGRAM MAY NOT BE USED FOR COMMERCIAL PURPOSES

Reprint Pricing

50 copies = $336.00
100 copies = $420.00
200 copies = $494.00
300 copies = $571.00
400 copies = $655.00
500 copies = $732.00

Plain Covers

$108.00 for first 100 copies
$18.00 each add'l 100 copies

Reprint Color

($70.00/100 reprints)

Shipping

Within the U.S. - $15.00 up to the first 100 copies and $15.00 for each additional 100 copies

Outside the U.S. - $30.00 up to the first 100 copies and $30.00 for each additional 100 copies

Tax

U.S. and Canadian residents add the appropriate tax or submit a tax exempt form.

Payment

● MC ● VISA ● Discover ● American Express

Account # / / Exp. Date

Name

Address Dept/Rm

City State Zip Country

Telephone

Signature

Ship to

Name

Address Dept/Rm

City State Zip Country

Telephone

Use this form to order reprints. Publication fees, including color separation charges and page charges will be billed separately, if applicable.

Payment must be received before reprints can be shipped. Payment is accepted in the form of a check or credit card; purchase orders are accepted for orders billed to a U.S. address.

Prices are subject to change without notice.

For quantities over 500 copies contact our Healthcare Dept. For orders shipping in the US and Canada: call 410-528-4396, fax your order to 410-528-4264 or email it to Meredith.Doviak@wolterskluwer.com. Outside the US: dial 44 1829 772756, fax your order to 44 1829 770330 or email it to Christopher.Bassett@wolterskluwer.com.

MAIL your order to:
Lippincott Williams & Wilkins
Author Reprints Dept.
351 W. Camden St.
Baltimore, MD 21201

FAX:
410.528.4434

For questions regarding reprints or publication fees,
E-MAIL:
reprints@lww.com

OR **PHONE:**
1.866.903.6951

For *Rapid Ordering* go to: www.lww.com/periodicals/author-reprints