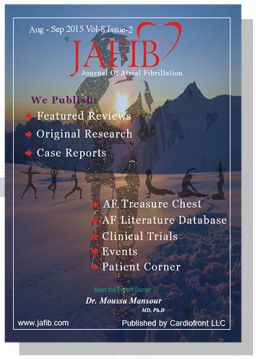
JAFIB
Featured Review
Journal of Atrial Fibrillation



www. jafib.com

Review And Insights Into The Bleeding Mechanism Incited By Antithrombotic Therapy: Mechanistic Nuances Of Dual Pro-Hemorrhagic Substrate Incorporating Drug-Induced Microvascular Leakage

Petras Stirbys MD, PhD

The Department of Cardiology, Hospital of Lithuanian University of Health Sciences , Kaunas Clinic, Kaunas, Lithuania.

Abstract

In patients with atrial fibrillation antithrombotic prophylaxis for stroke is associated with an increased risk of bleeding. Cerebrovascular risk-benefit ratio for oral anticoagulation therapies continues to be debated. Macro and/or microhematomas as well as visible or cryptic ones may appear unexpectedly in any anatomic region.

The diagnostic and prognostic value of subcutaneous hematomas (petechia, ecchymosis, bruise) potentially predisposing intracerebral micro- or macrobleeding might be reconsidered. Hypothetically, subcutaneous hemorrhagic events are "transparent" signs and reflect the coexistence of remote vulnerable sites that are potential bleeding sources. Obviously vigilance is needed for early signs of drug-related petechiae evaluation to determine whether it is a local/superficial subtlety or a systemic problem. Any bleeding complication, regardless of its scale and anatomical location, might be treated as a worrisome clinical symptom requiring subtle correction of antithrombotic regimen. The focus of this article is to review the current knowledge of drug-related hemorrhage with special emphasis on underlying mechanisms and links between the visible bleeding (predominantly subcutaneous) and remote (such as cerebral) hemorrhagic sources. To mitigate inappropriate therapy, we should consider new conceptual insights and more individualized approaches to achieve an optimal balance of efficacy and safety. We hypothesize that bleeding complications occur as a result of two factors – impact of antithrombotic drugs and related detrimental effect on microvascular network. Most likely the microvasculature undergoes pro-hemorrhagic medication stress leading to unfavorable vascular wall "fenestration" with ensuing consequences. If so, it suggests the presence of dual substrate responsible for hemorrhagic events.

Introduction

Atrial fibrillation (AF) is the most common rhythm disturbance worldwide. As a non-life threatening arrhythmia it carries a great risk of ischemic stroke along with severe hemorrhagic events, especially when oral antithrombotic drugs (OAD) are instituted. Untreated, AF increases the risk of ischemic stroke fivefold making stroke the leading complication of AF.[1] Eighty percent of strokes are caused by arterial occlusion of cerebral arteries, whereas the remaining twenty percent are caused by intracerebral hemorrhages.[2] However, although clinically intriguing, antithrombotic therapy can act like a double edged sword with both beneficial and adverse effects.

Meanwhile oral antithrombotic therapy (OAT) remains the best treatment option to prevent cardioembolism in AF.[3] Drug-related hematomas as a concomitant "metastatic ectopy" may simultaneously occur subcutaneously, in the brain or in any other topographic location of the human body. Cutaneous or subcutaneous hemorrhagic areas may cover lower extremities, neck, buttocks and may also affect large areas. Such therapeutic endpoints should not be interpreted as "innocent" symptoms. Spontaneous bruising is important but the bruise should be over 3 cm in size to be significant.[4]

We would like to focus on conspicuous subcutaneous hematomas appearing as a result of antithrombotic treatment. These hematomas as precursors may herald more severe bleeding in other locations, predominantly in the brain. Thus, such correlation likely raises the risk of bleeding expansion. For this reason intracerebral microbleeding and subcutaneous hemorrhage may represent a peculiar clinical relationship. Regarding the mechanism of hemorrhage the OADs presumably affect both blood coagulation parameters and microvascular/angiogenic factors. Thus, better understanding is needed to avoid excessive out-of-control bleeding.

This review is part of the ongoing efforts to improve clinical results in patients undergoing antithrombotic therapy.

Background And Reflections

The prevention and containment of bleeding is a major

Disclosures:
None.

Corresponding Author:
Petras Stirbys MD, PhD,
A. Ramanausko-Vanago str. 4-7,
49306 Kaunas,
Lithuaniany

therapeutic goal in patients suffering from AF. Recently Fischer et al.[5] have offered a new term – mixed cerebrovascular disease which incorporates clinical and subclinical syndromes including ischemic stroke, intracerebral hemorrhage and cerebral microbleeds. The balance between the risk of bleeding and the risk of stroke needs to be estimated for each patient based on patient's values and preferences, as well as awareness of the prognostic implications of bleeding.[3]

Hematomas range from small and relatively benign to severe, including life-threatening ones. Numerous reports have amply demonstrated clinical emergency due to acute or subacute intracranial, intracerebral, retropharyngeal or intramuscular hemorrhagic outbreaks resulting in serious brain damage, life-threatening suffocation, anemia and/or death.[6-14] The findings of Risch and colleagues.[15] confirm that intracranial, muscular and soft-tissue hemorrhagic events exclusively occur in patients who receive OADs.

Underlying mechanisms of coagulation-bleeding physiology implicate very complex biological interactions between blood and tissue factors.[16] even without interference of OADs. Sporadic reports suggest that microhemorrhages are preferential focuses of intracerebral hemorrhage (ICH) in patients receiving OAD, most likely because the drug unmasks ICH that would otherwise remain asymptomatic.[17] Extensive anticoagulant effect is well-established as a powerful risk factor for ICH.[8] Fortunately the menace of AF-related stroke and hemorrhage in most cases is amenable to medical control at least when conventional OAD medication is applied.

Ubiquity of multiple hemorrhagic foci actually alerts clinicians and their patients as well. However, it is still unclear where the bleeding starts first – subcutaneously (superficially), intracerebrally, selectively anywhere or uniformly in the whole body. In general, unnoticed or ignored subcuticular hemorrhage may negatively influence the clinical course of AF therapy. Moreover, there is a concern that patients as well as their physicians may become reconciled to the trivial petechiae, eventually paying no attention to alarming abnormality. Aspirational target of medical community is zero hazard ratio – an ideal bleeding-free as well as stroke-free clinical course of AF.

With regard to bleeding substrate one can hypothesize that we deal with the integral bleeding circuit with individual components of favorable/prohemorrhagic conditions. Responsible mechanisms are not clear and may relate to individual effects of local vasculopathy subtlets - bleeding per diapedesis in proportion to medication, microvascular disintegration, capillary fragility, etc. Recently Altman .[19] has emphasized that bleeding is an eventuality that occurs in places of "locus minoris resistentiae". This might serve as a starting point for some clinical revelations, specifically to verify the etiology of the hemorrhage. It seems, at least hypothetically, that OADs activate microvascular "weakest links" residing in the soft tissues.

Clinical Reality

Under physiological circumstances the concerted action of platelets, active biological blood components, and tissue factors influence the coagulation cascade and maintains hemostasis.[3] Interfered by specific drugs the coagulation system is affected significantly; that is why antithrombotic therapy faces many challenges.

Any bleeding events are categorized as major and minor by anatomical site.[20] Major bleeding is defined as an intracranial hemorrhage, a decrease in blood hemoglobin level of more than 5.0 g/dL, the need for a transfusion of two or more units of blood, the need for corrective surgery, or any combination of these events ;[21] minor bleeding is defined as a subcutaneous ecchymosis or hematoma, gastrointestinal bleeding, or bloody sputum.

The study of Guo and colleagues.[21] demonstrated that there were no thromboembolic events in elderly patients taking OAD, but 33% of them had bleeding complications. According to Goldstein and Greenberg[12] while bleeding is the major risk, not all bleeding events are equally damaging. Recently Jacobs and colleagues[22] have suggested that anticoagulation with inherent period of supratherapeutic and subtherapeutic effects provoke both chronic microemboli and microbleeds; patients with prior ischemic cerebral injury may be more likely to experience repetitive or worsened injury with longer anticoagulation use.

There are disparities in efficacy between pharmacologic groups of OADs. Regarding the intracerebral bleeding there is a perception that aspirin is effective and is safer than warfarin.[23] The incidence of major hemorrhage with aspirin monotherapy is approximately 1.5% per year.[24] In general, antiplatelet treatment is likely safer, as antiplatelet agents carry a substantially lower risk of bleeding.[25, 26] Conversely, vitamin K's antagonist warfarin therapy has been shown to be more effective than aspirin for the prevention of stroke in patients with AF.[27] Unfortunately, there is no absolutely "safe" INR (international normalized ratio) even with the conventionally therapeutic range.[8] New anticoagulant dabigatran is associated with a surprisingly enhanced risk for both thrombo-embolism and bleeding disorders clearly indicating the importance of accurate follow-up of AF patients.[28] However, the only reversal option for dabigatran is emergency dialysis which can be a challenge when it comes to patients with a threatening ICH.[29] This procedure takes time which is why the therapeutic efficacy may be overtaken by intense bleeding. Several OADs, i.e. dual or triple therapy and their interactions have been shown to increase the risk of serious bleeding.[6, 30] Warfarin interaction with at least one drug was considered in a retrospective study as the main contributor to bleeding in almost half of the cases.[31]

Controversies Of Intracerebral Microbleeding

The increasing use of antithrombotic drugs in an aging population is associated with a dramatic increase in the incidence of intracerebral hemorrhage.[15,32] A group of clinicians[33] have stated that the count of microbleeds or macrobleeds predicts an increased risk of hemorrhagic stroke in survivors of ICH. With anticoagulation, however, the benefit has to be balanced against an increased risk of ICH, which is the most feared complication of anticoagulation, causing death or severe disability in up to 75% of patients.[13] Increasing use of warfarin to prevent cardioembolic stroke due to AF has led to a fivefold increase in the incidence of anticoagulant-related ICH, which now accounts for approximately 15% of all ICH.[34] It is a paradox that many of these patients at the highest risk of cardioembolic stroke are also at the highest risk of ICH.[35] Recent work in the field.[29] has recognized that OAT related intracerebral hemorrhage rises up more questions than answers.

Cerebral microbleeds (CMB) are small chronic brain hemorrhages which are likely caused by structural abnormalities of the small vessels of the brain.[31] Yates et al.[36] declared that microscopic hemorrhages occur in the setting of impaired small vessel integrity, commonly due to either hypertensive vasculopathy or cerebral amyloid angiopathy. Recently Shoamanesh and colleagues.[37] have demonstrated that microbleeds on magnetic resonance imaging were associated

with evidence in prior bleeding in 81% (e.g. hemosiderin-laden macrophages or old hematoma).

Vascular release of blood components in the absence of trauma in orally anticoagulated patients defines the clinical entity being of great interest. In literature, the risk/benefit ratio of anti-thrombotic drugs in individuals with CMBs is controversial.[31] Microbleeds which have long been perceived as harmless and irrelevant in disease development, were found in 23 percent of patients with Alzheimer's disease in the review of five studies;[38] a previous study showed that 6.5% of healthy 45-to 50-year olds have microbleeds, whereas 35.7% of people 80 and older have them. Some investigators have concluded that CMBs are not just an incidental finding revealed by new neuroimaging technology.[39] From a pathophysiological standpoint, CMBs appear to be the expression of a hemorrhage-prone state of the brain, which might carry greater risk of ICH.[31]

There are some controversies related to whether the intracerebral microbleeding is harmful or not. The presence of cognitive decline symptoms in anticoagulated patients is also debated. Most cerebral microhemorrhages identified by gradient-echo imaging are clinically silent.[39, 40] Some investigators, however, have shown that microvascular damage plays a key role in cognitive impairment, especially in older patients.[31] Because CMBs reflect small areas of hemorrhage, and are common in both ischaemic and intracerebral hemorrhage,[41] they have caused concern regarding the risk of future intracerebral hemorrhage.[39] Kakar and colleagues[39] have postulated that CMBs develop over time and are common in populations likely to be exposed to antithrombotic drugs. Anti-platelet agents, traditionally safer than anticoagulants, are associated with an increased risk of ICH, especially in subjects with high number of CMBs.[42, 43] Apparently every anticoagulated individuum possesses its own hemorrhagic scenario. The ability to concentrate or disseminate the hemorrhagic foci in specific anatomic regions represents the phenomenon to yet be elucidated.

The rate of intracerebral hemorrhage in patients given OADs has been hypothesized to be the inherent risk multiplied by a factor determined by intensity of anticoagulation.[44] It looks like weak points are or provoked with the anticoagulation as a parent material which activates a bleeding cascade. Specifically, increase in dose often leads to exacerbation of hemorrhage or to proliferation of "weakest points". When collated, multilateral interrelationship of "high anticoagulation - high vulnerability - high risk" might be traced.

Clinical Importance Of Subcutaneous Bleeding

In individuals under antithrombotic treatment clinicians often observe multiple hemorrhages scattered across the patient's body. Anatomical distribution of bleeding sites varies within wide range allowing the hemorrhagic foci to overlap several territories. Hemorrhagic events sometimes are represented by simultaneous appearance of subcutaneous and intraorganic/intraparenchymal hematomas, both overt and/or cryptic. It is still unclear whether subcutaneous hemorrhage is strongly associated with systemic bleeding. Again, it is worth to discuss whether the subcutaneous bleeding is a clinically remarkable symptom or not. Also the recurrence of subcutaneous bleeding is to be estimated mostly in terms of its diagnostic and prognostic value. No doubt, we deal with the plural, i.e. loci minores resistentiae which, according to the manifestation pattern might be defined as sporadic, multiple, migrans, cryptic and/or visible. In theory, the patient without visible hematomas is not free from supposed hemorrhage. If so, petechia likely coexists with other bleeding sources, e.g. intracerebral microhematomas. Literature sources available do not provide a distinct relationship in this regard.

Some investigators[31, 35, 39] have declared that CMBs are potential predictors of future intracerebral hemorrhage. In turn, by extrapolation, clinical significance of CMBs likely is comparable to subcutaneous hemorrhage as far as their etiological similarity. In other words, subcutaneous bleeding foci are important not per se, but may reflect the presence of intracerebral hemorrhage and vice versa. Thus, any bleeding events wherever they are most often reflect the common anticoagulation status and increased bleeding risk in any possible anatomical site. If so, the entire body of the patient comprises the feasibility of hemorrhagic outbreaks at any time and in any topographic area, especially under excessive anticoagulation.

There are no recommendations related to clinical strategy and how to care for the noticed subcutaneous bleeding, particularly when it is extensive. Physical removal of OADs even provisionally might be a risky maneuver unless worsening signs do appear. Reduced anticoagulation particularly in repeat bleeding events and subsequent monitoring of blood markers is beneficial. Some clinical reports suggest that optimal antithrombotic therapy selection for patients with AF must be mainly accomplished based on individual and accurate risk stratification for both thromboembolism and hemorrhage during therapy, not based only on the risks before treatment.[21] The cautious approach to OAT in patients with bleeding risk is suggested by many clinicians.[31, 44]

Co-Participation Of Anticoagulation And Vascular Disintegrity: New Insights

The precise mechanism by which anticoagulation increases the incidence of intracerebral bleeding is unclear.[7] Immediate precipitants could be as trivial as an interval of relatively higher blood pressure or minor mechanical stress such as the shear forces of vigorous head shaking;[8] one idea is that the anticoagulation may cause subclinical brain hematomas to grow to clinical importance. Classical bleeding supportive causes might be taken into account, e.g. per diapedesis or per microvascular rupture resulting in extravasation of blood components. Bleeding likely evolves from both the intensity of medication and individual characteristics of small vascular peculiarities. Herein we do not analyze the subclinical or clinical injuries originating from physical impact.

Meanwhile the hypothesis of "locus minoris resistentiae" provides the best explanation of the behavior of bleeding-prone locations. However, this approach fails to disclose the cause and the mechanism of hemorrhagic foci migration across the anticoagulated human body. We can observe sporadic, multiple or single hemorrhagic spots (bruises) which may appear or reappear in the same site or in alternating regions. Likely the local architectonic and structural tissue specificities along with "anticoagulant-induced vasculopathy" reflect the clinical threats which might be construed and incorporated into the discussion. Seemingly, unique tissue/vascular conditions may determine different bleeding intensity in specific vulnerable/susceptible anatomic sites.

Under physiological conditions the breakage of the endothelial barrier leads to exposure of extravascular tissue factor which provides additional hemostatic protection.[16] Consequently, drug-induced vascular disintegration conjoined and reinforced by the loss of blood's clotting capability eventually cause blood spillage into surrounding

tissues most often in a form of imbibition. So, it is reasonable to suspect that dual substrate, i.e. both the antithrombotic agent and microvascular abnormality most likely are responsible for the bleeding event. Conceptually AODs open the bleeding sources which were tightly closed before the therapy. These gates likely resist until the crucial shift in concentration of AOD's is reached; then bleeding of non-traumatic origin is launched. In other words the extravasation of clotting-free blood is impossible without vasogenic component. Findings of Charidimou and Werring[35] have shown that OADs provide direct evidence of blood leakage from pathologically fragile small vessels. The contributing role of local vascular disease, such as cerebral amyloid angiopathy, is favored by observation of a high frequency of this angiopathy in individuals with warfarin-related ICH.[29] Negative influence of OADs on capillary or pre-capillary endothelial cells, including their disintegration, might be conceivable. However, individual characteristics of small vascular peculiarities as an indispensable cofactor presumably influence the bleeding intensity from patient to patient under the same antithrombotic regimen. Taken together it could be suspected that AODs, especially in high-doses, may have direct impact on microvascular damage, at least enhanced capillary or precapillary permeability.

Despite percolation of blood's "corpuscles" and plasma through the capillary the cardiovascular system represents a unique, securely sealed and well-organized entity. From a purely mechanical point of view functional harmony of the closed circulatory system might be characterized by an axiom: no vascular leakage, no sanguination regardless of the presence of blood thinners.

Epilogue And Conclusions

As stressed by Yates et al.[36] microscopic hemorrhages occur due to impaired small vessel integrity. It supports our conceptual viewpoint. It could be suspected that anticoagulant milieu do facilitate capillary fragility and potentiate microvascular damage, most likely its auto-rupture. Deductively, the microvasculature undergoes pro-hemorrhagic medication stress. The exposure to critical dose of OADs, in the absence of physical impact, might explain the mechanism of sanguination. Eventually, the higher the serum drug concentration is the greater risk of blood eruption. Figuratively speaking the vascular "fenestration" (of iatrogenic origin), abundantly adverse, is a critical condition, otherwise the bleeding will not be evoked by any blood thinner even when using maximum dosage.

In a metaphorical sense, loss of coagulability as such covers just a half or two thirds of the "distance" until bleeding is initiated. The remaining "distance" – up to the bleeding manifestation - is surmounted and finalized by drug-dependent microvascular changes.

Clinical observations demonstrate the potential presence of multiple hemorrhagic sources in different anatomic regions. In reality these focal points are dormant unless OADs are introduced. More surprising is the fact that bleeding foci may change their topographic areas, as if migrating occasionally with a period of clinical latency eventually related to anticoagulation regimen.

Despite the fact that almost all subcutaneous hematomas resolve spontaneously without clinical consequences their presence and reappearance should not be underestimated or ignored. Therapeutic vigilance is needed to eliminate two risks – bleeding and cardioembolism. Hence, OAD's dose re-adjusting strategy in response to anticoagulation fluctuations should be the best solution of clinical problem. An ideal approach – treatment lege artis with painstaking control of both bleeding and cardioembolism is the goal of clinical practice. In summary, the following methods should be considered:

1) Enhanced surveillance for visible bleeding sites in patients during their routine visits should be taken into account.

2) To maintain adequate anti-coagulated status the risk/benefit ratio should be considered and care should be individualized, especially in those patients with visible subcutaneous hemorrhage.

3) Dose re-adjusting strategy to reach ne plus ultra therapeutic condition is highly recommended.

4) Under the thromboprophylaxis the bleeding likely stems from dual substrate – impact of antithrombotic drug which, in turn, evokes detrimental effect on microvascular network.

5) Further studies are needed to improve the understanding of the mechanism of drug-related hemorrhage.

References

1. Lip GY. Atrial fibrillation in 2011: stroke prevention in AF. Nat.Rev. Cardiol. 2012; 9:71-7310.1038/nrcardio.2011.203 [PubMed]. [Cros Ref]
2. De Meyer SF, Stoll G, Wagner DD, Kleinschnitz C. von Willebrand factor an emerging target in stroke therapy. Stroke 2012; 43:599-606.
3. De Caterina R, Husted S, Wallentin L et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013; 109(4):569-579.
4. Palmer RL. Excessive bleeding and bruising. Chapter 146. In: Clinical methods: the history, physical, and laboratory examinations. Ed by H.K. Walker. W.D. Hall, J.W. Hurst; 3rd edition. Boston: Butterworths; 1990.
5. Fischer M, Vasilevko V, Cribbs DH. Mixed cerebrovascular disease and the future of stroke prevention. Transl Stroke Res 2012; 3 (Suppl 1):39-51. doi: 10.1007/s12975-012-0185-6
6. Gasse C, Hollowell J, Meier C, Haefell W. Drug interactions and risk of acute bleeding leading to hospitalization or death in patients with chronic atrial fibrillation treated with warfarin. Thromb Haemost. 2005; 94:537-543.
7. Quinones-Hinojosa A, Gulati M, Singh V, Lawton MT. Spontaneous intracerebral hemorrhage due to coagulation disorders. Neurosurg Focus 2003; 15(4):E3.
8. Hart RC, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. Facts and hypothesis. Stroke 1995; 26:1471-1477.
9. Ozpolat B, Yilmaz MA, Yucel E. Lingual hematoma threatening airway obstruction in a patient on oral anticoagulation with warfarin. Blood Coagulation and Fibrinolysis 2007; 18(6):575-576.
10. Butler ML, Dewan RW. Subcutaneous hemorrhage in a patient receiving anticoagulant therapy: an unusual EMG complication. Arch Phys Med Rehabil 1984; 65(11):733-734.
11. Dineen RA, Lewis NR and Altaf N. Small bowel infarction complicating rectus sheath hematoma in an anticoagulated patient. Med Sci Monit 2005; 11:CS57-CS59.
12. Goldstein JW, Greenberg SM. Should anticoagulation be resumed after intracerebral hemorrhage? Cleve Clin J Med. 2010; 77(11):791-799.
13. Fang MC, Go AS, Chang Y et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med. 2007; 120:700-705. [PMCfree article] [Pub Med]
14. Triaridis S, Tsiropoulos G, Rachovitsas D, Psillas G, and Vital V. Spontaneous haematoma of the pharynx due to a rare drug interaction. Hippokratia 2009; 13(3):175-177.
15. Risch O, Alfidja A, Muliez A, Amani AH et al. Severe non-traumatic bleeding events detected by computed tomography: do anticoagulants and antiplatelet agents have a role? J Thorac Cardiovasc Surg 2014; 9:166. doi:10.1186/s13019-

014-0166-9
16. Mackman N. The role of tissue factor and factor VIIa in hemostasis. Anesth Analg 2009; 108(5):1447-1452. doi: 10.1213/ane.0b013e31819bceb1
17. Lee G, Kwon S, Kang D. Warfarin induced hemorrhage associated with microbleeds. J Clin Neurol. 2008; 4:131-133.
18. Hylek A, Singer D. Risk factor for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med. 1994; 120:897-902.
19. Altman R. New oral anticoagulants: are coagulation units still required? Thrombosis J 2014; 12:3. doi: 10.1186/1477-9560-12-3
20. Hermandez I, Baik SH. Pinera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med. 2014 Nov 3. doi: 10.1001/jamainternmed. 2014.5398 [PubMed]
21. Guo Y, Wu O, Zhang L. Yang T et al. Antithrombotic therapy in very elderly patients with atrial fibrillation: is it enough to assess thromboembolic risk? Clin Interv Aging. 2010; 5:157-162.
22. Jacobs V, Woller SC, Stevens S, May HT et al. Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. Heart Rhythm 2014; 11(12):2206-2213.
23. Chung-Wah Siu, Lip GYH, Kwok-Fai Lam, Hung-Fat Tse. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. Heart Rhythm 2014; 11(8):1401-1408.
24. Katzan JL. Antiplatelet agents in secondary stroke prevention. Clevelend Clinic Center for Continuing Education 2009. www.clevelandclinicmeded.com/ medicalpubs/diseasemanagement/neurology/antiplatelet-agents/
25. Viswanathan A, Rakich SM, Engel C et al. Antiplatelet use after intracerebral hemorrhage. Neurology. 2006; 66:206-209.
26. Flaherry ML, Tao H, Haverbusch M et al. Warfarin use leads to larger intracerebral hematomas. Neurology 2008; 71:1084-1089.
27. Waldo A. Why aspirin should not be used for atrial fibrillation stroke prevention: video interview. Youtube. June 27, 2012/ Interviewed by M.T. Hills.
28. Sorensen R, Gislason G, Torp-Pedersen C, Olesen JB et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BJM open 2013:3(5). doi: 10.1136/bmjopen.2013-002758
29. Terecoasa E, Tiu C, Huertas N, de Lecinana MA. Oral anticoagulation related intracerebral hemorrhage: more questions than answers. Romanian J Neurol. 2012; 11(1):13-23.
30. Jonsson A, Spigset O, Jacobsson I, Hagg S. Cerebral haemorrhage induced by warfarin: the influence of drug-drug interactions. Pharmacoepidemiol Drug Saf. 2007; 16:309-315.
31. Martinez-Raminez S, Greenberg SM and Viswanathan A. Cerebral microbleeds: overview and implications in cognitive impairment. Alzheimer's Research and Therapy 2014; 33. doi:10.1186/alzrt263.
32. Charidimou A, Shakeshaft C, Werrig DJ. Cerebral microbleeds on magnetic resonance imaging and anticoagulant-associated intracerebral hemorrhage risk. Front Neurol. 2012; 3:133-doi: 10.3389/fneur.2012.00133
33. Greenberg SM, O'Donnell HC, Schaefer PW, Kraft E. MRI detection of new hemorrhages: potential marker of progression in cerebral amyloid angiopathy. Neurology 1999; 53:1135-1138.
34. Flaherry ML, Kissela B, Wao D et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007; 68:116-121.
35. Charidimou A, Werring DJ. Cerebral microbleeds: detection, mechanisms, and clinical challenges. Future Neurol. 2011; 6(5):587-611.
36. Yates PA, Villemagne VL, Ellis KA, Desmond PM et al. Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations. Front Neurol 2013; 4:205 doi: 10.3389/fneur.2013.00205
37. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovasc Dis 2011; 32:528-3410.1159/000331466 [PubMed] [Cross ref]
38. Chan A. Brain microbleeds provide clue for Alzheimer's origins [Internet] [Cited 2014 Nov 14] Available from: http://www.nbcnews.com/id/41413221/ns/health-alzheimers_disease/lt/brain-microbleeds-provide-clue-alzheimers-originals/ .
39. Kakar P, Charidimou A and Werring DJ. Cerebral microbleeds: a new dilemma in stroke medicine. JRSM Cardiovasc Dis. Nov 2012; 1(8):20480040124754. doi:10.1177/204800401247454
40. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke. 2004; 35:1415-1420.
41. Werring D. Cerebral microbleeds. Pathophysiology to clinical practice, United Kingdom. SAGE Publications, 2011.
42. Soo Yo, Yang SR, Lam WW, Wong A et al. Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. J Neurol 2008; 255:1679-1688.
43. Biffi A, Halpin A, Towfight A, Gilson A et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. Neurology 2010; 75:693-698.
44. Wintzen AR, De Jonge H, Loeliger EA, Botts GTAM. The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. Ann Neurol. 1984; 16:533-558.