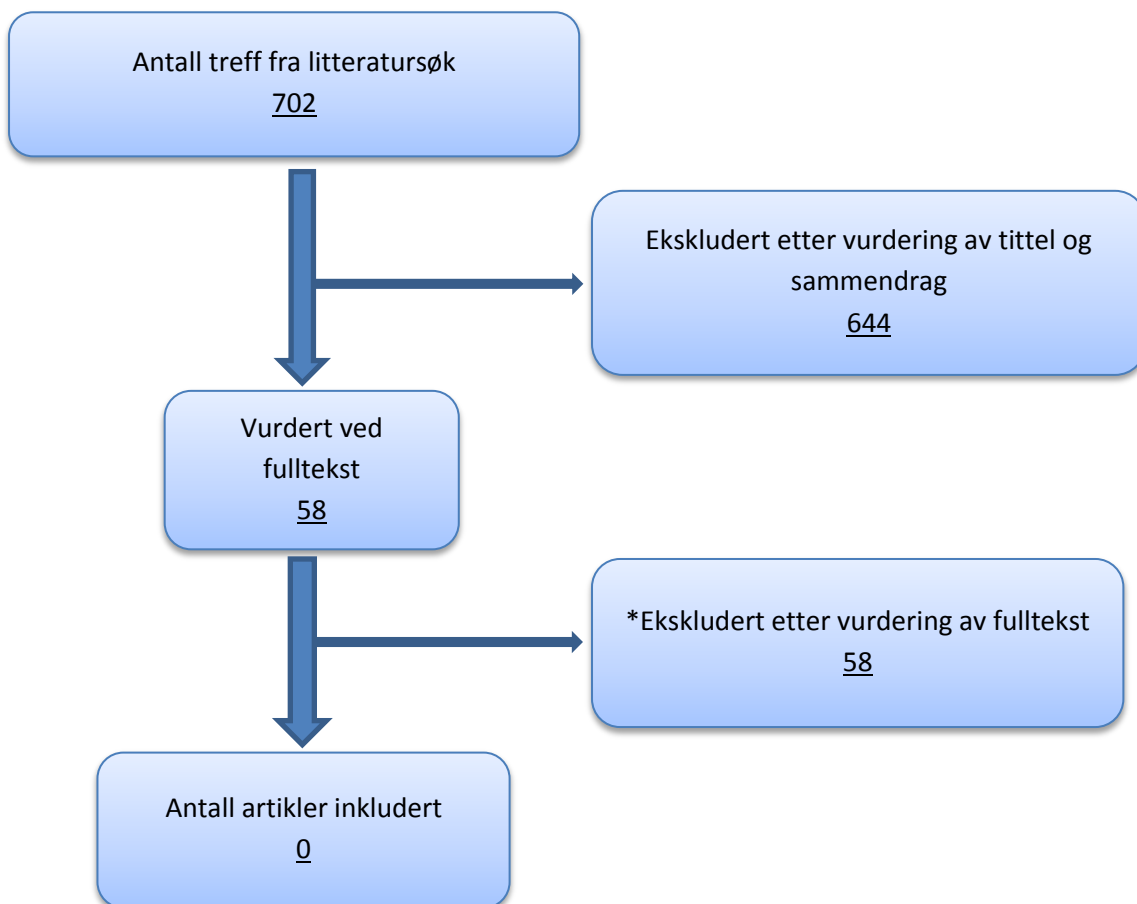


Dokumentasjonsark: Nasjonal faglig retningslinje for hjerneslag

Spørsmål: Har pasienter som har gjennomgått hjerneblødning nytte av platehemmende behandling?

| | | |
|----------|---|------------------------------|
| P | Pasienter med hjerneblødning | |
| I | Platehemming | Dato for søk: 9.11.2015 |
| C | Ingen behandling | Søk oppdatert dato: |
| O | Hjerneinfarkt, hjerneblødning, mortalitet, major blødning | Bibliotek: Helsedirektoratet |



*Årsak til eksklusjon av studier etter vurdering av fulltekst:

Tabell 2. Ekskluderte referanser. Sammendraget/tittel funnet relevant, ekskludert etter vurdering av fulltekst av artikkel.

| Forfatter | År | Kommentar/begrunnelse for eksklusjon |
|---|-----------|--|
| Alhusban & Fagan, | 2011 | Studiepopulasjon ikke overførbar til PICO |
| Alreja, Chandrasekaran, Trikalinos, & Rothberg, | 2011 | Intervensjon ikke overførbar til PICO |
| Al-Shahi Salman, Lee, Frantzias, & Lyden, | 2014 | Møter ikke PICO |
| Ansara, Shiltz, & Slavens, | 2012 | Møter ikke PICO |
| Bath, Geeganage, Bath, & Sprigg, | 2011 | Studiepopulasjon ikke overførbar til PICO |
| Behrouz & Sadat-Hosseiny, | 2015 | Møter ikke PICO |
| Benbassat, Baumal, & Herishanu, | 2011 | Ikke SR |
| Bergman, | 2011 | Møter ikke PICO |
| Berkowitz, Westover, Bianchi, & Chou, | 2014 | Møter ikke PICO |
| BMJ Publishing Group, | 2015 | Møter ikke PICO |
| Bokura & Yamaguchi, | 2013 | Intervensjon ikke overførbar til PICO |
| Cameron et al., | 2014 | Møter ikke PICO |
| Campbell, Sen, Yadla, Jabbour, & Jallo, | 2010 | Møter ikke PICO |
| Chalouhi et al., | 2014 | Møter ikke PICO |
| Chari, Clemente Morgado, & Rigamonti, | 2014 | Studiepopulasjon ikke overførbar til PICO |
| Cordonnier, | 2011 | Ikke SR; Intervensjon ikke overførbar til PICO |
| De Gautard & Perrier, | 2014 | Ikke SR; kun tilgjengelig på fransk |
| De Rooij, Dankbaar, Frijns, & Rinkel, | 2012 | Møter ikke PICO |

| | | |
|--|------|--|
| De Rooij, Rinkel, Dankbaar, & Frijns, | 2013 | Møter ikke PICO |
| Degos et al., | 2013 | Ikke SR; møter ikke PICO |
| d'Esterre & Lee, | 2010 | Møter ikke PICO |
| Diener, Weimar, & Weber, | 2010 | Ikke SR; møter ikke PICO |
| Dinicolantonio et al., | 2013 | Møter ikke PICO |
| R. Flynn & Doney, | 2011 | Duplikat |
| R. W. Flynn, MacDonald, Murray, & Doney, | 2010 | Aktuell SR. Inkluderer kun en observasjonsstudie som er aktuell for PICO og den er lagt til i trefflisten for RCT-søket. |
| Gandhi et al., | 2014 | Ikke SR; møter ikke PICO |
| Gorelick & Ruland, | 2010 | Møter ikke PICO |
| Gregoire et al., | 2010 | Møter ikke PICO |
| Grzegorski, Andrzejewska, & Kazmierski, | 2015 | Møter ikke PICO |
| Hofmeijer, Kappelle, & Klijn, | 2015 | Ikke SR |
| Horie et al., | 2014 | Konferanse abstrakt; møter ikke PICO |
| James, Palys, Lomboy, Lamm, & Simon, | 2013 | Ikke SR; møter ikke PICO |
| Kamal, Naqvi, Husain, & Khealani, | 2011 | Studiepopulasjonen ikke overførbart til PICO |
| Kamal, Naqvi, Husain, & Khealani, | 2011 | Duplikat |
| Kirshner, | 2014 | Studiepopulasjonen ikke overførbart til PICO |
| Liu & Li, | 2015 | Utfallsmål ikke overførbart til PICO |
| Lovelock et al., | 2010 | Utfallsmål ikke overførbart til PICO |
| Malloy, Kanaan, Silva, & Donovan, | 2013 | Kun konferanse abstrakt; møter ikke PICO |
| Malloy, Kanaan, Silva, & Donovan, | 2013 | Duplikat |
| Mok & Kim, | 2015 | Ikke SR |

| | | |
|--|------|--|
| Naidech, Batjer, & Bernstein, | 2011 | Møter ikke PICO |
| Niu, Yang, Xing, Guo, & Yang, | 2014 | Studiepopulasjonen ikke overførbar til PICO |
| Olmos, Marin, Docampo, & Martin, | 2012 | Møter ikke PICO |
| Palacio et al., | 2015 | Møter ikke PICO |
| Peng et al., | 2014 | Feil intervensjon; møter ikke PICO |
| Schorr & Nitschmann, | 2010 | Kun på Tysk; møter ikke PICO |
| Srivastava, | 2010 | Ikke SR; studiepopulasjonen ikke overførbar til PICO |
| Tan et al., | 2015 | Studiepopulasjonen ikke overførbar til PICO |
| Thompson et al., | 2010 | Møter ikke PICO |
| Vergouwen, Etminan, Ilodigwe, & MacDonald, | 2011 | Møter ikke PICO |
| J. N. Wang & Wei, | 2013 | Kun på Kinesisk |
| Z. Wang, Soo, & Mok, | 2014 | Ikke SR; studiepopulasjonen ikke overførbar til PICO |
| A. Warkentin, M. Donadini, F. Spencer, W. Lim, & M. Crowther, | 2012 | Studiepopulasjonen ikke overførbar til PICO |
| A. E. Warkentin, M. P. Donadini, F. A. Spencer, W. Lim, & M. Crowther, | 2012 | Duplikat |
| Watanabe, Siddiqui, & Qureshi, | 2012 | Feil intervensjon; studiepopulasjonen ikke overførbar til PICO |
| Zazulia, | 2015 | Ikke SR |
| Zhang et al., | 2015 | Studiepopulasjonen ikke overførbar til PICO |
| Zhou et al., | 2012 | Studiepopulasjonen ikke overførbar til PICO |

Fullstendig referanseliste (inkluderte og ekskluderte referanser).

- Al-Shahi Salman, R., Lee, R., Frantziar, J., & Lyden, P. (2014). The risk of intracerebral haemorrhage (ICH) growth by time of diagnostic scan after ICH symptom onset: Individual patient data meta-analysis (IPDMA). *International Journal of Stroke*, 9, 6. doi: <http://dx.doi.org/10.1111/ijis.12374>
- Alhusban, A., & Fagan, S. C. (2011). Secondary prevention of stroke in the elderly: A review of the evidence. *American Journal Geriatric Pharmacotherapy*, 9(3), 143-152. doi: <http://dx.doi.org/10.1016/j.amjopharm.2011.04.002>
- Alreja, G., Chandrasekaran, D., Trikalinos, T., & Rothberg, M. (2011). Oral anticoagulants for secondary prophylaxis of stroke in coronary artery disease and cerebrovascular accident. *Journal of the American College of Cardiology*, 1), E1509. doi: <http://dx.doi.org/10.1016/S0735-1097%2811%2961509-X>
- Ansara, A. J., Shiltz, D. L., & Slavens, J. B. (2012). Use of cilostazol for secondary stroke prevention: an old dog with new tricks? *Annals of Pharmacotherapy*, 46(3), 394-402. doi: <http://dx.doi.org/10.1345/aph.1Q420>
- Bath, P. M. W., Geeganage, C. M., Bath, M. W., & Sprigg, N. (2011). Balance between preventing pulmonary embolism and causing symptomatic intracerebral haemorrhage with anticoagulation thromboprophylaxis in early ischaemic stroke: A systematic review and metaanalysis of randomised controlled trials. *Cerebrovascular Diseases*, 31, 184. doi: <http://dx.doi.org/10.1159/000329448>
- Behrouz, R., & Sadat-Hosseiny, Z. (2015). Pharmacological agents in aneurysmal subarachnoid hemorrhage: Successes and failures. *Clinical Neuropharmacology*, 38(3), 104-108. doi: <http://dx.doi.org/10.1097/WNF.0000000000000085>
- Benbassat, J., Baumal, R., & Herishanu, Y. (2011). Treatment of acute ischemic stroke in patients with cerebral microbleeds: A decision analysis. *Qjm*, 104(1), 73-82. doi: <http://dx.doi.org/10.1093/qjmed/hcq119>
- Bergman, D. (2011). Preventing recurrent cerebrovascular events in patients with stroke or transient ischemic attack: The current data. *Journal of the American Academy of Nurse Practitioners*, 23(12), 659-666 658p. doi: 10.1111/j.1745-7599.2011.00650.x
- Berkowitz, A. L., Westover, M. B., Bianchi, M. T., & Chou, S. H. (2014). Aspirin for acute stroke of unknown etiology in resource-limited settings: a decision analysis. *Neurology*, 83(9), 787-793. doi: <http://dx.doi.org/10.1212/WNL.0000000000000730>
- BMJ Publishing Group. (2015). Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study (Vol. 49, pp. 1414-1422 1419p): BMJ Publishing Group.
- Bokura, H., & Yamaguchi, S. (2013). Diagnosis and treatment of brain microbleeds. [Japanese]. *Brain and Nerve*, 65(7), 825-830.
- Cameron, C., Coyle, D., Richter, T., Kelly, S., Gauthier, K., Steiner, S., . . . Wells, G. (2014). Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ Open*, 4(6), e004301. doi: <http://dx.doi.org/10.1136/bmjopen-2013-004301>
- Campbell, P. G., Sen, A., Yadla, S., Jabbour, P., & Jallo, J. (2010). Emergency reversal of antiplatelet agents in patients presenting with an intracranial hemorrhage: a clinical review. *World Neurosurgery*, 74(2-3), 279-285. doi: <http://dx.doi.org/10.1016/j.wneu.2010.05.030>
- Chalouhi, N., Zanaty, M., Jabbour, P. M., Starke, R. M., Tjoumakaris, S. I., Rosenwasser, R. H., & Gonzalez, L. F. (2014). Intracerebral hemorrhage after pipeline embolization: Management of antiplatelet agents and the case for point-of-care testing--case reports and review of literature. *Clinical Neurology & Neurosurgery*, 124, 21-24. doi: <http://dx.doi.org/10.1016/j.clineuro.2014.06.021>

- Chari, A., Clemente Morgado, T., & Rigamonti, D. (2014). Recommencement of anticoagulation in chronic subdural haematoma: A systematic review and meta-analysis. *British Journal of Neurosurgery*, 28(1), 2-7. doi: <http://dx.doi.org/10.3109/02688697.2013.812184>
- Cordonnier, C. (2011). Brain microbleeds: More evidence, but still a clinical dilemma. *Current Opinion in Neurology*, 24(1), 69-74. doi: <http://dx.doi.org/10.1097/WCO.0b013e328341f8c0>
- d'Esterre, C. D., & Lee, T. Y. (2010). Effect of dipyridamole during acute stroke: exploring antithrombosis and neuroprotective benefits. *Annals of the New York Academy of Sciences*, 1207, 71-75. doi: <http://dx.doi.org/10.1111/j.1749-6632.2010.05801.x>
- De Gautard, G., & Perrier, A. (2014). [Antiplatelet agents in secondary prevention of stroke]. *Revue Medicale Suisse*, 10(446), 1902, 1904-1907.
- De Rooij, N. K., Dankbaar, J. W., Frijns, C. J. M., & Rinkel, G. J. E. (2012). Delayed cerebral ischemia after subarachnoid hemorrhage: A systematic review of clinical, laboratory and radiological predictors. *Cerebrovascular Diseases*, 33, 351-352. doi: <http://dx.doi.org/10.1159/000339538>
- De Rooij, N. K., Rinkel, G. J. E., Dankbaar, J. W., & Frijns, C. J. M. (2013). Delayed cerebral ischemia after subarachnoid hemorrhage: A systematic review of clinical, laboratory, and radiological predictors. *Stroke*, 44(1), 43-54. doi: <http://dx.doi.org/10.1161/STROKEAHA.112.674291>
- Degos, V., Westbroek, E. M., Lawton, M. T., Hemphill, J. C., 3rd, del Zoppo, G. J., & Young, W. L. (2013). Perioperative management of coagulation in nontraumatic intracerebral hemorrhage. *Anesthesiology*, 119(1), 218-227. doi: <http://dx.doi.org/10.1097/ALN.0b013e318297c18a>
- Diener, H. C., Weimar, C., & Weber, R. (2010). Antiplatelet therapy in secondary stroke prevention--state of the art. *Journal of Cellular & Molecular Medicine*, 14(11), 2552-2560. doi: <http://dx.doi.org/10.1111/j.1582-4934.2010.01163.x>
- Dinicolantonio, J. J., Lavie, C. J., Fares, H., Menezes, A. R., O'Keefe, J. H., Bangalore, S., & Messerli, F. H. (2013). Meta-analysis of cilostazol versus aspirin for the secondary prevention of stroke. *American Journal of Cardiology*, 112(8), 1230-1234. doi: <http://dx.doi.org/10.1016/j.amjcard.2013.05.067>
- Flynn, R., & Doney, A. (2011). Antithrombotic medicines following intracerebral haemorrhage: where's the evidence? *Therapeutic Advances in Drug Safety*, 2(5), 205-211. doi: <http://dx.doi.org/10.1177/2042098611415457>
- Flynn, R. W., MacDonald, T. M., Murray, G. D., & Doney, A. S. (2010). Systematic review of observational research studying the long-term use of antithrombotic medicines following intracerebral hemorrhage. *Cardiovascular therapeutics*, 28(3), 177-184. doi: <http://dx.doi.org/10.1111/j.1755-5922.2009.00118.x>
- Gandhi, C. D., Bulsara, K. R., Fifi, J., Kass-Hout, T., Grant, R. A., Almandoz, J. E. D., . . . Jayaraman, M. V. (2014). Platelet function inhibitors and platelet function testing in neurointerventional procedures. *Journal of Neurointerventional Surgery*, 6(8), 567-577. doi: <http://dx.doi.org/10.1136/neurintsurg-2014-011357>
- Gorelick, P. B., & Ruland, S. (2010). Cerebral vascular disease. *Disease-A-Month*, 56(2), 39-100. doi: <http://dx.doi.org/10.1016/j.disamonth.2009.12.003>
- Gregoire, S. M., Jager, H. R., Yousry, T. A., Kallis, C., Brown, M. M., & Werring, D. J. (2010). Brain microbleeds as a potential risk factor for antiplatelet-related intracerebral haemorrhage: hospital-based, case-control study. *Journal of Neurology, Neurosurgery & Psychiatry*, 81(6), 679-684. doi: <http://dx.doi.org/10.1136/jnnp.2009.198994>
- Grzegorski, T., Andrzejewska, N., & Kazmierski, R. (2015). Reversal of antithrombotic treatment in intracranial hemorrhage--A review of current strategies and guidelines. *Neurologia i Neurochirurgia Polska*, 49(4), 278-289. doi: <http://dx.doi.org/10.1016/j.pjnns.2015.06.003>
- Hofmeijer, J., Kappelle, L. J., & Klijn, C. J. (2015). Antithrombotic treatment and intracerebral haemorrhage: between Scylla and Charybdis. *Practical Neurology*, 15(4), 250-256. doi: <http://dx.doi.org/10.1136/practneurol-2015-001104>

- Horie, N., Kaminogo, M., Hirao, T., Fukushima, M., Izaki, A., Mori, K., . . . Nagata, I. (2014). Impact of the type of prior antithrombotic agents on secondary hemorrhagic stroke: Location, severity and outcome. *Stroke*, *45*.
- James, R. F., Palys, V., Lomboy, J. R., Lamm, J. R., Jr., & Simon, S. D. (2013). The role of anticoagulants, antiplatelet agents, and their reversal strategies in the management of intracerebral hemorrhage. *Neurosurgical Focus*, *34*(5), E6. doi: <http://dx.doi.org/10.3171/2013.2.FOCUS1328>
- Kamal, A. K., Naqvi, I., Husain, M. R., & Khealani, B. A. (2011). Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Cochrane Database of Systematic Reviews*(1), CD008076. doi: <http://dx.doi.org/10.1002/14651858.CD008076.pub2>
- Kamal, A. K., Naqvi, I., Husain, M. R., & Khealani, B. A. (2011). Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Stroke*, *42*(6), e382-e384. doi: <http://dx.doi.org/10.1161/STROKEAHA.111.614842>
- Kirshner, H. S. (2014). Review: Dual-antiplatelet therapy does not reduce recurrent stroke but can increase ICH. *ACP Journal Club*, *160*(2), 1-1 1p.
- Liu, S., & Li, C. (2015). Antiplatelet Drug Use and Cerebral Microbleeds: A Meta-analysis of Published Studies. *Journal of Stroke & Cerebrovascular Diseases*, *24*(10), 2236-2244. doi: <http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.05.022>
- Lovelock, C. E., Cordonnier, C., Naka, H., Al-Shahi Salman, R., Sudlow, C. L., Edinburgh Stroke Study, G., . . . Rothwell, P. M. (2010). Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. *Stroke*, *41*(6), 1222-1228. doi: <http://dx.doi.org/10.1161/STROKEAHA.109.572594>
- Malloy, R. J., Kanaan, A. O., Silva, M. A., & Donovan, J. L. (2013). Evaluation of antiplatelet agents for secondary prevention of stroke using mixed treatment comparison meta-analysis. *Clinical Therapeutics*, *35*(10), 1490-1500.e1497. doi: <http://dx.doi.org/10.1016/j.clinthera.2013.09.004>
- Malloy, R. J., Kanaan, A. O., Silva, M. A., & Donovan, J. L. (2013). The use of antiplatelet agents in secondary prevention of stroke: A network meta-analysis. *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy*, *33* (10), e187. doi: <http://dx.doi.org/10.1002/phar.1356>
- Mok, V., & Kim, J. S. (2015). Prevention and Management of Cerebral Small Vessel Disease. *Journal of Stroke*, *17*(2), 111-122. doi: <http://dx.doi.org/10.5853/jos.2015.17.2.111>
- Naidech, A. M., Batjer, H. H., & Bernstein, R. A. (2011). Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology*, *76*(18), 1607. doi: <http://dx.doi.org/10.1212/WNL.0b013e318219dc1b>
- Niu, P. P., Yang, G., Xing, Y. Q., Guo, Z. N., & Yang, Y. (2014). Effect of cilostazol in patients with aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Journal of the Neurological Sciences*, *336*(1-2), 146-151. doi: <http://dx.doi.org/10.1016/j.jns.2013.10.027>
- Olmos, V. P., Marin, V. M., Docampo, L. I., & Martin, A. J. M. (2012). The risk of bleeding in patients receiving therapeutic anticoagulation and antiangiogenic therapy. *Cancer and Chemotherapy Reviews*, *7*(2), 78-82.
- Palacio, S., Hart, R. G., Pearce, L. A., Anderson, D. C., Sharma, M., Birnbaum, L. A., & Benavente, O. R. (2015). Effect of addition of clopidogrel to aspirin on stroke incidence: Meta-analysis of randomized trials. *International Journal of Stroke*, *10*(5), 686-691. doi: <http://dx.doi.org/10.1111/ijis.12050>
- Peng, W., Yang, J., Wang, Y., Wang, W., Xu, J., Wang, L., & Xing, Z. (2014). Systematic review and meta-analysis of randomized controlled trials of xingnaojing treatment for stroke. *Evidence-based Complementary and Alternative Medicine*, *2014*(210851). doi: <http://dx.doi.org/10.1155/2014/210851>
- Schorr, K., & Nitschmann, S. (2010). [Acetylsalicylic acid in the primary and secondary prevention of vascular disease]. *Internist*, *51*(10), 1330, 1332. doi: <http://dx.doi.org/10.1007/s00108-010-2723-1>

- Srivastava, P. (2010). Optimization of antiplatelet/antithrombotic therapy for secondary stroke prevention. *Annals of Indian Academy of Neurology*, 13(1), 6-13. doi: <http://dx.doi.org/10.4103/0972-2327.61270>
- Tan, S., Xiao, X., Ma, H., Zhang, Z., Chen, J., Ding, L., . . . Hong, H. (2015). Clopidogrel and aspirin versus aspirin alone for stroke prevention: A meta-analysis. *PLoS ONE [Electronic Resource]*, 10(8). doi: <http://dx.doi.org/10.1371/journal.pone.0135372>
- Thompson, B. B., Bejot, Y., Caso, V., Castillo, J., Christensen, H., Flaherty, M. L., . . . Smith, E. E. (2010). Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology*, 75(15), 1333-1342. doi: <http://dx.doi.org/10.1212/WNL.0b013e3181f735e5>
- Vergouwen, M. D. I., Etmnan, N., Ilodigwe, D., & MacDonald, R. L. (2011). Lower incidence of cerebral infarction correlates with improved functional outcome after aneurysmal subarachnoid hemorrhage. *Journal of Cerebral Blood Flow and Metabolism*, 31(7), 1545-1553. doi: <http://dx.doi.org/10.1038/jcbfm.2011.56>
- Wang, J. N., & Wei, J. J. (2013). [Advances in the pathogenesis and treatment of neurosurgical emergency with coagulation disorders]. *Chung-Kuo i Hsueh Ko Hsueh Yuan Hsueh Pao Acta Academiae Medicinae Sinicae*, 35(5), 576-580. doi: <http://dx.doi.org/10.3881/j.issn.1000-503X.2013.05.017>
- Wang, Z., Soo, Y. O., & Mok, V. C. (2014). Cerebral microbleeds: is antithrombotic therapy safe to administer? *Stroke*, 45(9), 2811-2817. doi: <http://dx.doi.org/10.1161/STROKEAHA.114.004286>
- Warkentin, A., Donadini, M., Spencer, F., Lim, W., & Crowther, M. (2012). Bleeding risk in randomized controlled trials comparing warfarin and aspirin: A systematic review and meta-analysis. *American Journal of Hematology*, 87, S157. doi: <http://dx.doi.org/10.1002/ajh.23168>
- Warkentin, A. E., Donadini, M. P., Spencer, F. A., Lim, W., & Crowther, M. (2012). Bleeding risk in randomized controlled trials comparing warfarin and aspirin: a systematic review and meta-analysis. *Journal of Thrombosis & Haemostasis*, 10(4), 512-520. doi: <http://dx.doi.org/10.1111/j.1538-7836.2012.04635.x>
- Watanabe, M., Siddiqui, F. M., & Qureshi, A. I. (2012). Incidence and management of ischemic stroke and intracerebral hemorrhage in patients on dabigatran etexilate treatment. *Neurocritical Care*, 16(1), 203-209. doi: <http://dx.doi.org/10.1007/s12028-011-9591-y>
- Zazulia, A. (2015). Antiplatelet and anticoagulant therapy after intracerebral hemorrhage. *Neurologic Clinics*, 33(2), 329-345. doi: <http://dx.doi.org/10.1016/j.ncl.2014.12.005>
- Zhang, Q., Wang, C., Zheng, M., Li, Y., Li, J., Zhang, L., . . . Yan, C. (2015). Aspirin plus clopidogrel as secondary prevention after stroke or transient ischemic attack: a systematic review and meta-analysis. *Cerebrovascular Diseases*, 39(1), 13-22. doi: <http://dx.doi.org/10.1159/000369778>
- Zhou, Y. H., Wei, X., Lu, J., Ye, X. F., Wu, M. J., Xu, J. F., . . . He, J. (2012). Effects of combined aspirin and clopidogrel therapy on cardiovascular outcomes: a systematic review and meta-analysis. *PLoS ONE [Electronic Resource]*, 7(2), e31642. doi: 10.1371/journal.pone.0031642