Antithrombotic therapy in the Netherlands: new insights from nationwide data

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CHAPTER

Summary and General discussion

The study aims of the studies presented in this thesis can be summarized as taking a snapshot of the status of antithrombotic therapy in the Netherlands in recent years in order to understand how and how well this therapy was performed and find out what could be further improved. As antithrombotic therapy may be required for various indications, the focus of this thesis was mainly on ischemic stroke prevention for atrial fibrillation (AF), but antithrombotic therapy in the pregnant and COVID-19 population was also covered. Below, the main findings of each study presented in the thesis are again summarized, and some other relevant unresolved issues of antithrombotic therapy were discussed as future perspectives. In addition, possibilities as well as limitations of using big data for conducting clinical research were also discussed, using the Dutch nationwide data as an example.

Summary of the main findings

The study presented in **Chapter 2** aimed to investigate time trends in patient characteristics, anticoagulation treatment, and prognosis of patients with incident nonvalvular atrial fibrillation (NVAF) in the Netherlands. In a cohort study design, incident NVAF patients initially recognized through a hospitalization between 2014 and 2018 were included to compare their patient characteristics, anticoagulation treatment, and one-year prognosis between years. The main findings of this study included: (1) the baseline characteristics of patients with incident AF remained broadly the same among calendar years; (2) oral anticoagulants (OACs) were increasingly prescribed within one year after incident AF diagnosis, and direct oral anticoagulant (DOAC) replaced vitamin K antagonist (VKA) as the first option of OAC; (3) the one-year risks of both ischemic stroke and major bleeding decreased.

The study presented in **Chapter 3** aimed to examine anticoagulant prescription patterns and prognosis of NVAF patients by sex, baseline CHA_2DS_2-VASc and HAS-BLED score. This study was actually a further investigation of the study presented in **Chapter 2**, which found sex differences in the distribution of components of CHA_2DS_2-VASc score and HAS-BLED score, as well as clinical outcomes. The main findings of this study included: (1) there was similar anticoagulant therapy between the sexes, but male patients received more antiplatelet drugs with a higher major bleeding risk than the female; (2) anticoagulant prescription was in general guided by both baseline CHA_2DS_2-VASc score and HAS-BLED score, but about 20% of the patients who had a high CHA_2DS_2-VASc score and low HAS-BLED score remained not anticoagulated; (3) both scores were associated with ischemic stroke and major bleeding risks, but a CHA_2DS_2-VASc score <2 well identified the patient group who had an annual ischemic stroke risk <1%, including those with comorbid cancer or kidney diseases; (4) NVAF patients with comorbid cancer

or kidney diseases were less anticoagulated but had a higher major bleeding risk than those with the same CHA_2DS_2-VASc score and HAS-BLED score.

The study presented in **Chapter 4** aimed to investigate the persistence with OAC and its association with prognosis among NVAF patients. Before conducting this study it was unknown whether suboptimal persistence with OAC was associated with increased risk of ischemic stroke, although numerous studies had reported a suboptimal anticoagulant compliance/persistence in AF patients[1]. The main findings of this study included: (1) persistence with OAC or with the initial DOAC was suboptimal, and a higher risk of non-persistence was observed in the early stage after the start of DOAC use compared to the later stage; (2) several baseline characteristics including baseline CHA_2DS_2-VASc score were associated with persistence pattern; and (3) being non-persistent with OAC was associated with poor efficacy of ischemic stroke prevention.

The study presented in **Chapter 5** aimed to provide comprehensive epidemiology of coexisting AF and cancer. By taking the complete Dutch population as the source population, prevalence and incidence of having one condition among individuals with the other condition, as well as their time trends and associations with all-cause mortality were examined. The main findings of this study included: (1) AF and cancer are commonly coexisting, and the prevalence of having one condition among those with the other was increasing in recent years; (2) compared to the general population, having one condition is associated with an increased risk of developing the other, and both risks are the highest during the first three months; (3) the types of cancer that are more likely to develop after AF are in line with the most frequent cancer types in the general population, while individuals with some types of cancer are noticeably more likely to develop AF than those with other cancer types; (4) newly developing cancer is associated with increased all-cause mortality among AF patients, and vice versa, but the strength of the association with mortality varies by cancer type.

After confirming the burden of coexisting AF and cancer, the study presented in **Chapter 6** aimed to describe potential changes in anticoagulant therapy shortly after having both AF and cancer, and time trends in long-term anticoagulation and prognosis of this patient population. The main findings of this study included: (1) there were distinct patterns of changes in anticoagulant therapy after having both AF and cancer between those who had AF first and those who had cancer first; (2) there were differences in several baseline patient characteristics (including HAS-BLED score or prior major bleeding, valvular heart diseases, recent venous thromboembolism (VTE), and previously received types of anticoagulant) between types of anticoagulants received after having

both AF and cancer; (3) from 2015 to 2019 patients were increasingly anticoagulated within the one year after having both AF and cancer, which was driven by increasing use of DOACs, but about 25% remained not anticoagulated; (4) prognosis of the complete patient population within one year after having both AF and cancer remained broadly the same over time, but the risk of intracranial hemorrhage (ICH) and VTE seemed to decreased in those who had AF first; (5) the absolute one-year risk of major bleeding still remained notably high (≈3%).

The study presented in **Chapter 7** investigated antithrombotic therapy during pregnancy, which aimed to describe patterns of antithrombotic therapy and maternal/fetal/newborn outcomes in the Netherlands. The main findings of this study included: (1) the proportion of receiving anticoagulant remained similar between 2013 and 2019 which was dominated by low-molecular-weight heparin (LMWH), while antiplatelet drug prescription significantly increased from <1% in 2013 to about 5% in 2019; (2) in the context of such an increase in antiplatelet agent prescription over the years, there was a constant maternal risk of both bleeding and thromboembolic complications during pregnancy, but unlike the continuous increase in risk of gestational diabetes, risk of preeclampsia/eclampsia significantly decreased in the most recent years; (3) over the same time periods there was similar risk of stillbirth and neonatal bleeding, but decreasing risk of perinatal death, congenital abnormalities, and low birthweight among the live births.

Although the study presented in **Chapter 8** again included AF patients as the study population, instead of examining anticoagulant therapy, this study actually employed anticoagulant therapy for AF as a proxy for early anticoagulation therapy for COVID-19. The study investigated the association between pre-existing chronic anticoagulation and survival during the COVID-19 pandemic, aiming to provide insight into the potential role of anticoagulant in the early stage of COVID-19. The main findings of this study included: (1) excess mortality was observed in the Dutch population in 2020 but only during the first and second wave of COVID-19 pandemic, and the magnitude was lower in the second wave than the first wave; (2) during the first wave of COVID-19 pandemic, the magnitude of excess mortality in the anticoagulated population was significantly lower than that in the general population and the diabetic population; (3) during the second wave of COVID-19 pandemic, although there was no statistically significant difference in excess mortality between populations, excess mortality in the anticoagulated population still appeared to be numerically lower than the diabetic population.

Implications and future perspectives

Ischemic stroke prevention for atrial fibrillation

Anticoagulant therapy for ischemic stroke prevention in AF patients no doubt also follows the principle of rational medication use[2]. Clearly, to achieve the best prognosis, it requires that the medication type, timing, dosage, and patient group are all optimally chosen. This seems easy to achieve, but is actually challenging, at least for NVAF patients. Unlike patients with valvular AF (*i.e.*, AF with prosthetic mechanical heart valves or moderate-to-severe mitral stenosis, although debates exist about this definition[3]), who in general need anticoagulation therapy with VKA being the preferred type of OACs, the decision on anticoagulation therapy for NVAF patients currently is mainly determined by the CHA_2DS_2-VASc score, and DOAC is generally preferred over VKA[4]. However, NVAF patients are actually heterogeneous, raising concerns about whether one recommendation fits all situations. Since the study periods in the above-mentioned studies for AF covered the time period when DOAC replaced VKA as the first-line option of OAC for NVAF and when the CHA_2DS_2-VASc score was introduced to guide anticoagulation therapy, calendar year, to some extent, could be seen as an instrumental variable to study whether changes in anticoagulation therapy led to changes in clinical outcomes. According to **Chapter 2**, the NVAF patient population indeed experienced less ischemic stroke and major bleeding in recent years, which might be, at least partly, related to the observed changes in anticoagulant therapy, including the increasing use of OAC and the replacement of VKA by DOAC. This is promising, as it confirmed the findings observed in clinical trials that DOAC was at least noninferior but safer than VKA[5-8]. However, the improvement observed at population level does not mean that each NVAF patient was optimally anticoagulated. First of all, suboptimal persistence with OAC remains an issue, which was associated with increased risk of ischemic stroke (**Chapter 4**). Even leaving out this issue, there was difference in some patient characteristics between those who received DOAC and those who received VKA, which already suggested potential concerns of prescribing DOAC to patients with certain characteristics (**Chapter 2**). For example, patients who received VKA were older than those who received DOAC, and according to results of a recent trial, switching VKA to DOAC in frail older patients with NVAF might lead to more bleeding complications[9]. Comorbid cancer, kidney diseases, and sex differences, are also patient characteristics that might affect the optimal anticoagulation strategy. In **Chapter 3**, NVAF patients with either cancer or kidney diseases were less anticoagulated but experienced more bleeding events than the complete NVAF patient population with the same CHA_2DS_2-VASc score and HAS-BLED score. Together with the findings from the further investigations into anticoagulation therapy and prognosis among NVAF patients with cancer (**Chapter 6**), these results suggest that NVAF patients

with cancer or kidney diseases might not be optimally managed, and thus efforts are needed to search for a better prediction of bleeding risk in order to optimally anticoagulate these AF subpopulations. Given the heterogeneity of cancer and its association with AF (**Chapter 5**), this would not be an easy task. The studies presented in this thesis did not cover other comorbidities, but similar investigations are also needed to examine how well the current anticoagulation strategy works among patients with other comorbidities, and whether there is room for improvement, including choice of OAC, dosage, performance of the CHA_2DS_2-VASc score and HAS-BLED score. Regarding sex disparity, different cutoffs of the CHA_2DS_2-VASc score were already used for different sexes[4], but the observed sex difference in concurrent antiplatelet drug warrants a further examination. As "drugs don't work in patients who don't take them"[10], efforts should also be put into the improvement of medication compliance/persistence. Since in the era of VKA, in some countries there were well developed anticoagulation management services (such as anticoagulation clinics in the Netherlands), it might be a good idea to consider whether there is a role of switching the monitoring function of such services from VKA to DOAC. In a recent study, receiving pharmacist-managed anticoagulation care appeared to be associated with fewer adverse events[11]. This remains a direction to explore, although cost-effectiveness and the subpopulation of DOAC users who might benefit from monitoring should also be carefully considered. In short, findings from the studies presented in the thesis suggest that ischemic stroke prevention for AF in the Netherlands in recent years was improving overall, but there is still room for improvement. Searching for optimal anticoagulation strategies for several specific AF subpopulations and further improving medication compliance and persistence remain the main directions for improvement.

Antithrombotic therapy during pregnancy

Although only a low proportion of pregnant women would actually require antithrombotic therapy, the relevance of this topic is no less than that of ischemic stroke prevention for AF. The relevance mainly comes from the importance of using antiplatelet drugs (*i.e.*, low-dose aspirin) for preventing preeclampsia which affects about 2-10% pregnant women and is associated with unfavored maternal and fetal/newborn outcomes[12]. Traditionally, due to ethical issues and safety of the unborn babies, including pregnant women into a clinical trial is often complex and at least not easy. As a result, high-quality evidence for pregnant women is often lacking which hinders decision making[13]. The increasing availability of large-scale perinatal registries perhaps offers an alternative way to supplement clinical evidence, although randomized controlled trials often are still desired compared to observational studies. The study presented in **Chapter 7** is an example, which for the first time provided a comprehensive overview of antithrombotic

therapy as well as maternal/fetal/newborn outcomes in the general pregnant population. As descriptive epidemiology, the findings present abundant information about who were receiving antithrombotic agents and how these medications were prescribed during pregnancy, as well as on the relevant clinical outcomes. Such information may benefit patient education and decision making regarding antithrombotic therapy. In addition, similar to the study design presented in **Chapter 2**, since during the study period low-dose aspirin was expected to increasingly use among pregnant population[14], calendar year here also severed as an instrumental variable to examine whether the advance led to changes in clinical outcomes of either the mother or the child. It is promising to see that with the increase in antiplatelet drug use, there was a decrease in both preeclampsia/eclampsia and low birthweight, which at population level confirmed the efficacy of low-dose aspirin for preeclampsia prevention observed in clinical trials[14,15]. Unlike antiplatelet treatment (*i.e.*, low-dose aspirin) for preeclampsia prevention, of which the efficacy and safety has been well established, there are still uncertainties surrounding anticoagulant therapy during pregnancy. Although LMWH is generally recommended when anticoagulant is indicated, whether it is beneficial for improving pregnancy outcomes among women with recurrent pregnancy loss is still unclear[16]. This question is rather relevant to know, as it may avoid overuse of LMWH during pregnancy. VKA, and especially DOAC, are generally recommended against during pregnancy, and the observed Dutch practice in **Chapter 7** suggested this recommendation was well followed, although there were still a few pregnant women who received more than two prescriptions of DOAC during pregnancy. To further educate women of reproductive age who were receiving chronic anticoagulant treatment is necessary to avoid unnecessary exposure to DOAC.

Antithrombotic therapy during the COVID-19 pandemic

The clinical research question behind the study presented in **Chapter 8** is whether there is a role of anticoagulant at the early stage of COVID-19. Although the COVID-19 pandemic was already over, and the availability of COVID-19 vaccines had made this clinical research question less relevant, the study presented an example of how routinely collected data could inspire causal hypotheses[17]. In the study presented in **Chapter 8**, excess mortality in a chronically anticoagulated population (*i.e.*, AF patients) in 2020 was compared to that in the populations that generally did not require anticoagulation therapy. Such a study design makes it not necessary to know who were actually with infected with SARS-CoV-2 (*i.e.*, misclassification), and also avoids a direct comparison between the anticoagulated population and the non-anticoagulated populations (*i.e.*, confounding by indication). Although the results would still require confirmation by a randomized controlled trial, it would be extremely helpful in a situation when evidence is urgently

needed while there is lack of other relevant data (*e.g.*, lack of COVID-19 diagnosis information due to limited testing capacity), as the study only required mortality statistics. This experience will help better prepare for the next pandemic.

Microdata from Statistics Netherlands

The studies presented in the thesis all used Microdata from Statistics Netherlands, mainly including diagnoses registered within hospitalizations, dates and causes of death, personal characteristics, and outpatient medication prescriptions. These data together make it possible to perform studies of clinical epidemiology, either cross-sectional or longitudinal. With linkage to other data sources (such as the Dutch perinatal registry in **Chapter 7**), more research topics are further feasible to investigate. The main strength of the microdata is the coverage of information generally at nationwide level and in continuous time periods. This makes it possible to consider the complete Dutch population as a single cohort, with available individual information about demographic characteristics, diseases, medications, and mortality. Since all the data were already de-identified, and they could only be accessed and analyzed in a remote virtual environment with private network, both the data and individual privacy were well protected. In addition, exporting results from the remote virtual environment would require a manual examination according to the prespecified output guideline to prevent potential disclosure. These measurements also contribute to strengths of the data.

However, similar to any other routinely collected data, no real-world data are perfect. A major concern about the Dutch data is misclassification. In the studies presented in the thesis, the data source only included medications prescribed in outpatient settings, and therefore medication prescribed during hospitalization would always be missing. The amount of each medication prescription was also unavailable, so extra assumptions had to be introduced to determine the time period of medication exposure. Actually, even when this information is available, filling a medication prescription would not always be equal to the actual intake of the medication. When identifying diseases in the studies, only diagnoses registered during hospitalizations were available to use, which would underrecognize mild diseases (which might be managed by general physicians in outpatient settings). This limitation can be somewhat mitigated by extending the time period for screening for the disease of interest, but often at the expense of shortening the follow-up period. Another issue is about selection bias, and the perinatal registry is a typical example. Since only deliveries with a gestational age ≥22 weeks are compulsory to register, information of pregnancy that failed to reach this cutoff would be missing and cannot be further investigated. Including more data sources and improving data quality no doubt will help address these issues, but more importantly, it is still possible to provide

research evidence by imperfect data with an appropriate study design plus appropriate interpretation.

Conclusions

Antithrombotic therapy for ischemic stroke prevention and for the pregnant women in the Netherlands in recent years was in general improving, although there is still room for further improvement. The nationwide data presents a highly valuable resource to perform observational studies to supplement evidence from clinical trials.

References

[1] Ozaki AF, Choi AS, Le QT, Ko DT, Han JK, Park SS, Jackevicius CA. Real-World Adherence and Persistence to Direct Oral Anticoagulants in Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. Mar 2020;13(3):e005969. doi:10.1161/CIRCOUTCOMES.119.005969

[2] Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny MP, Sheikh A. Medication Without Harm: WHO's Third Global Patient Safety Challenge. Lancet. Apr 29 2017;389(10080):1680-1681. doi:10.1016/S0140-6736(17)31047-4

[3] Lip GYH. Anticoagulation in Atrial Fibrillation and Rheumatic Heart Disease. N Engl J Med. Sep 15 2022;387(11):1036-1038. doi:10.1056/NEJMe2210187

[4] Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. Feb 1 2021;42(5):373-498. doi:10.1093/eurheartj/ehaa612

[5] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. Sep 17 2009;361(12):1139-51. doi:10.1056/NEJMoa0905561

[6] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. Nov 28 2013;369(22):2093-104. doi:10.1056/NEJMoa1310907

[7] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. Sep 15 2011;365(11):981-92. doi:10.1056/NEJMoa1107039

[8] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. Sep 8 2011;365(10):883-91. doi:10.1056/NEJMoa1009638

[9] Joosten LPT, van Doorn S, van de Ven PM, et al. Safety of Switching from a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients with Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial. Circulation. Aug 27 2023;doi:10.1161/CIRCULATIONAHA.123.066485

[10] Bonaccorso S, Sturchio JL. What information do patients need about medicines? Perspectives from the pharmaceutical industry. BMJ. Oct 11 2003;327(7419):863-4. doi:10.1136/bmj.327.7419.863

[11] Derington CG, Goodrich GK, Xu S, et al. Association of Direct Oral Anticoagulation Management Strategies With Clinical Outcomes for Adults With Atrial Fibrillation. JAMA Netw Open. Jul 3 2023;6(7):e2321971. doi:10.1001/jamanetworkopen.2023.21971

[12] Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. Lancet. Jul 24 2021;398(10297):341-354. doi:10.1016/S0140-6736(20)32335-7

[13] The Lancet H. To treat, or not to treat: the dilemma for pregnant women. Lancet Haematol. Feb 2019;6(2):e58. doi:10.1016/S2352-3026(19)30001-8

[14] Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. Aug 17 2017;377(7):613-622. doi:10.1056/NEJMoa1704559

[15] Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, Group PC. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. May 26 2007;369(9575):1791-1798. doi:10.1016/S0140-6736(07)60712-0

[16] Strandell A, Hellgren M. Time to stop routine prescription of low-molecular-weight heparin to women with recurrent pregnancy loss and inherited thrombophilia. Lancet. Jul 1 2023;402(10395):6-7. doi:10.1016/S0140-6736(23)01190-X

[17] Fox MP, Murray EJ, Lesko CR, Sealy-Jefferson S. On the Need to Revitalize Descriptive Epidemiology. Am J Epidemiol. Jun 27 2022;191(7):1174-1179. doi:10.1093/aje/kwac056