Antithrombotic therapy in the Netherlands: new insights from nationwide data

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CHAPTER

General introduction and outline of the thesis

Thromboembolic complications, either arterial or venous, remain a major public health burden[1]. Ischemic heart disease and stroke (most are ischemic[2]), as the top two leading causes of death globally[3], are both thromboembolic complications; some other leading causes of death, either noncommunicable diseases (such as cancer) or communicable diseases (such as infectious diseases), are also closely associated with thromboembolism[4-6]. The Coronavirus disease (COVID-19) pandemic has attracted great attention to thromboembolic complications, given the unexpectedly high risk of thromboembolic events observed in these patients[7-9]. Together they make thromboembolic complications prevalent conditions, and antithrombotic agents one of the most widely prescribed groups of medication[10].

Antithrombotic agents can be categorized as anticoagulants and antiplatelet agents, where anticoagulants comprise the heparin group, vitamin K antagonists (VKA), and direct oral anticoagulants (DOAC). In the past decade, the major advance in antithrombotic agents was the introduction of DOAC, which has predictable pharmacokinetics and pharmacodynamics and usually does not require regular monitoring[11]. Generally speaking, antithrombotic agents are used for prevention or treatment of thromboembolic complications. Indications for anticoagulant therapy mainly include atrial fibrillation (AF), valvular heart disease, venous thromboembolism (VTE), chronic coronary artery disease or peripheral artery disease[11, 12]. For antiplatelet agents, the indications include acute coronary syndrome, ischemic stroke/transient ischemic attack (TIA), peripheral arterial disease, or primary prevention in cardiovascular disease[13], although aspirin use for cardiovascular disease primary prevention has been decreasing with the increased use of statins[14].

The efficacy of antithrombotic therapy for most of these indications has already been established by numerous randomized controlled trials (RCTs)[15-18], but several issues still remain unresolved. Compared to other medication use (*e.g.*, antimicrobial therapy), a distinct feature of antithrombotic therapy is that the therapy is associated with adverse events of opposite directions (*i.e.*, thromboembolism versus hemorrhage), which makes it crucial to achieve a balance between the two during antithrombotic therapy. The situations when antithrombotic therapy is challenging are, unfortunately, often also the ones where high-quality evidence (such as RCTs) is lacking[19, 20]. Even when there are updated clinical guidelines based on high-quality evidence, their adherence in clinical practice becomes another issue[21]. In addition, indications for antithrombotic therapy are usually for a relatively long term, and thus medication persistence can be suboptimal[22]. All these barriers together hinder patients to obtain maximal benefit from antithrombotic therapy, which warrants evidence-based measures to improve their use. Most of these

issues cannot be resolved simply by conducting more RCTs, but warrant an evaluation of clinical practice which can be achieved with the increasing availability of large-scale routinely collected health data.

Ischemic stroke prevention for atrial fibrillation: Sex disparity, performance of CHA_2DS_2-VASc score and HAS-BLED score, anticoagulant persistence, and comorbid cancer

As the most common form of sustained cardiac arrhythmia[23], AF is also one of the most common indications for anticoagulant therapy[24], as it is associated with an overall five-fold increase in stroke risk[25]. In the past three decades, anticoagulation for ischemic stroke prevention gradually became one of the cornerstones of AF management[26]. The safety and efficacy of VKA for stroke prevention was first recognized[27], which was further found to be superior to aspirin for stroke prevention[28]. For non-valvular AF (NVAF, namely AF patients without valvular heart diseases), more favorable safety and efficacy profiles were observed for DOAC compared to VKA[29] which has replaced VKA as the first choice of oral anticoagulant for ischemic stroke prevention in recent years[25, 30]. Since 2010, two scoring systems (*i.e.*, the CHA_2DS_2-VASc score[31] and the HAS-BLED score[32]) have been adopted to guide anticoagulation for NVAF[33]. For valvular AF (*i.e.*, AF patients with prosthetic mechanical heart valves or moderate-to-severe mitral stenosis), however, VKA still remains the first therapeutic option due to the superior efficacy when compared with DOAC[12, 17, 34].

These advances indeed appear to have improved ischemic stroke prevention among AF patients, since declining incidence of AF related stroke was observed in recent years[35]. However, there are still some issues pending to address. Female patients were found to receive less anticoagulation than males even with a high CHA_2DS_2-VASc score, and they experienced more ischemic stroke[36]. The CHA_2DS_2-VASc score, which now plays a central role in determining whether a NVAF patient should receive anticoagulant therapy, was reported to perform suboptimally in AF patients with cancer and renal dysfunction[37, 38]. In addition, although DOAC users do not require regular control visits, there are concerns about suboptimal medication persistence considering their long-term use. According to a meta-analysis[39], there was lower real-world persistence with DOACs than that observed in RCTs, which was associated with poor clinical outcomes. As one of the conditions that complicate anticoagulation in AF patients[25], cancer is associated with increased risk of both thromboembolic complications and bleeding events[40, 41]. With cardio-oncology rapidly emerging as a new field, comorbid cancer in AF patients is increasingly recognized and considered[42]. However, AF patients with active cancer were

generally excluded from clinical trials, leaving a knowledge gap regarding the optimal anticoagulation strategy[43].

Antithrombotic therapy during pregnancy: What has happened in the DOAC era?

Antithrombotic therapy may be indicated during pregnancy: anticoagulant is prescribed mainly for prevention/treatment for thromboembolic complications, such as VTE[44], and antiplatelet agent is for prevention/treatment for placenta-mediated complications such as preeclampsia[45]. With an VTE incidence of about 1-2 in 1000[46] and a preeclampsia incidence of 2-10%[47], antithrombotic agent use is actually not uncommon among the pregnant population. Similar to any other medication use during pregnancy, safety of the unborn child should at all times be taken into account, which makes antithrombotic therapy distinct from that in the non-pregnant population. Unlike oral anticoagulation which is generally preferred for preventing thromboembolic complications in the non-pregnant population, low-molecular-weight heparin (LMWH) is recommended during pregnancy as it does not cross the placenta[44], while VKA (except for pregnant women with high-thrombotic-risk mechanical heart valves) and DOAC are recommended against due to potential teratogenicity[44, 48]. A timely switch from oral anticoagulation to LMWH is therefore necessary once pregnancy is confirmed[48]. However, it is unknown how well such a recommendation was followed now that DOAC has been increasingly used in the general population. Furthermore, there is a concern that some indications for LMWH use (such as recurrent pregnancy loss and inherited thrombophilia) are not truly supported by evidence[49]. In the past decade, another major advance in antithrombotic therapy during pregnancy was that low-dose aspirin was recommended for preeclampsia prevention[50, 51]. It remains unknown whether antiplatelet agent has been increasingly used during pregnancy and whether relevant clinical outcomes actually improved.

Antithrombotic therapy during the COVID-19 pandemic: Is there a role of anticoagulant therapy at the early stage of COVID-19?

Although the COVID-19 pandemic has ended, a lesson learned in the field of thrombosis and hemostasis is the crucial role of COVID-19 coagulopathy[52]. Several RCTs have confirmed the benefit of anticoagulation therapy for hospitalized COVID-19 patients, either in wards or in intensive care units, to prevent thromboembolic events, although the optimal doses differed between these two settings[53]. For most individuals with SARS-CoV-2 infection, they were actually asymptomatic or with only mild symptoms, but it remains unclear whether they would benefit from anticoagulation therapy for thromboembolism prophylaxis. Controversial findings were reported by observational

studies about the association between receiving anticoagulants before admission and COVID-19 prognosis[54], while all the RCTs that focused on anticoagulation among COVID-19 outpatients were early terminated due to low event rates[55-59].

Microdata from Statistics Netherlands: An epidemiologist's dream?

In the era of big data, population registry and electronic health records are often available at a large scale (*e.g.*, at nationwide level). This makes it an ideal resource for performing observational studies to provide evidence, although the fundamental limitations of observational research (such as confounding) still remain. An example is the various nationwide registries available in Denmark, where the entire country could be considered as a cohort, presenting every epidemiologist's dream[60, 61]. For most of the unresolved issues mentioned above, relevant nationwide data that cover almost everyone make it possible to include specific patient groups of a relatively large size, or to comprehensively examine relevant clinical practice in daily settings, thus providing insights that cannot be obtained from RCTs. In the Netherlands, Statistics Netherlands (in Dutch "Centraal Bureau voor de Statistiek", CBS) is a governmental institution that gathers and links de-identified individual data from various nationwide data sources. The Microdata provided by CBS, to some extent, also enable researchers to investigate the Dutch population (with a size of about 17 million) as a cohort for various research topics.

Outline of the thesis

This thesis presents several studies that used the Microdata from CBS to investigate the above-mentioned unresolved issues of antithrombotic therapy. Before focusing on the specific AF subpopulations, in **Chapter 2** antithrombotic therapy was first comprehensively examined in the complete AF population. In this chapter, incident NVAF patients in the Netherlands between 2014 and 2018 were identified and patient characteristics, anticoagulation treatment, and prognosis of the patients were compared between years. In **Chapter 3**, sex disparity, performance of the CHA_2DS_2-VASc score, and HAS-BLED score among NVAF patient population were further examined. In this chapter, incident NVAF patients in the Netherlands between 2015 and 2019 were identified and stratified by sex, levels of both the CHA_2DS_2-VASc score and HAS-BLED score, after which anticoagulant prescription pattern and prognosis were compared. A particular interest of the investigation was whether a low CHA_2DS_2-VASc score truly identified the NVAF patients who did experience a low absolute risk of ischemic stroke. In **Chapter 4**, persistence with oral anticoagulant was examined in a cohort of NVAF patients who initially received DOAC for ischemic stroke prevention. Whether poor persistence with oral anticoagulant was associated with increased risk of ischemic stroke was also investigated. Before diving into the study topic about antithrombotic therapy

among AF patients with comorbid cancer, in **Chapter 5** descriptive epidemiology of coexisting AF and cancer was presented. Prevalence of cancer among incident AF patients, and the risk of developing cancer after an incident diagnosis of AF among those without cancer at baseline were described, as well as their time trends. In addition, prevalence of AF among incident cancer patients, the risk of developing AF after an incident diagnosis of cancer among those without AF at baseline, and their time trends were also described. Besides, the association of developing cancer (or AF) after an incident diagnosis of AF (or cancer) with all-cause mortality was examined. After confirming the burden of coexisting AF and cancer, in **Chapter 6** anticoagulant therapy and prognosis in patients with AF and cancer was described and compared by years. In **Chapter 7**, the study population turned to the general pregnant population in the Netherlands between 2013 and 2019. Prescriptions of antithrombotic agent before and during pregnancy was described, overall, and by weeks of gestation period. Antithrombotic therapy as well as several maternal/fetal/newborn clinical outcomes were also compared by years. In **Chapter 8**, a population-based observational study was presented, which used preexisting chronic anticoagulation treatment as a proxy for anticoagulant therapy at the early stage of COVID-19 to study whether this was associated with better prognosis. Instead of directly comparing prognosis of individuals with and without preexisting chronic anticoagulation treatment, excess mortality was first evaluated by comparing the chronically anticoagulated population in 2020 to that in 2019, which was further compared between populations with and without chronic anticoagulation treatment in 2020. All studies together contributed to the above-mentioned unresolved issues of antithrombotic therapy, with the main findings being summarized in **Chapter 9**. As the findings of each study were already discussed separately in each chapter, in this chapter the findings were discussed in a more general way, and when applicable, with a brief introduction of other relevant unresolved issues of antithrombotic therapy. Possibilities as well as limitations of using big data for conducting clinical research were also discussed using the Dutch nationwide data as an example.

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