

Trends in Direct Oral Anticoagulants (DOACs) Use in the Community Setting According to Their Accessibility under National Health Basket in Israel: Real-World Data

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Background:

Although leading professional associations and regulatory authorities have long recommended Direct Oral Anticoagulants (DOACs) as first-line treatment over Vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF), treatment and prevention of Venous thromboembolism (VTE), and total hip/knee replacement (TKR/THR)¹⁻¹⁰, the rate of incorporation and accessibility of these drugs into the Israeli national health basket has been gradual and merely partial over the years (Figures 1,2).

Objective:

To describe the treatment patterns of oral anticoagulants in primary care, with emphasis on DOACs, as a function of the extent of their accessibility under public funding in the Israeli healthcare system and relative to different healthcare systems worldwide (Norway, England, and Canada).

Methods:

This retrospective cohort study based on Meuhedet Health Services database included patients who consumed at least one anticoagulant between 2013 and 2020 for the treatment of AF and/or VTE and/or TKR/THR. Demographic and clinical characteristics were described, including: age, gender, sector, socioeconomic status, diagnosis requiring anticoagulation, anticoagulant type with which treatment was initiated (DOACs, VKA, enoxaparin), adherence to anticoagulant treatment, annual CHADS₂ and CHA₂DS₂-VASC scores (for AF patient), etc. For patients diagnosed with more than one compelling condition for anticoagulation, a dominant diagnosis was assigned based on recommended anticoagulant treatment duration (AF, then VTE and then TKR/THR). The primary endpoint was the description of anticoagulants' use trends in Meuhedet (as a proxy of Israel) based on defined daily dose (DDD) and filled prescriptions per 1000 inhabitants, as compared to those seen in Norway, England, and Canada. Secondary endpoints included comparison between DOACs' clinical and reimbursement eligibility criteria for Meuhedet's naïve anticoagulants patients throughout the study period; identification of predictive factors for DOACs initiation over VKAs in AF patients using logistic regression; survival analysis examining AF patients mortality under DOACs vs. VKAs using Cox-regression test; and evaluation of Meuhedet's actual expenditure on DOACs relative to corresponding health basket funding between 2013-2020.

Results:

31,326 patients purchased at least one anticoagulant (DOAC, VKA, enoxaparin) during the study period. Half of them were AF patients. VKA use decreased from 76% in 2013 to 13% in 2020, and by the end of 2020, DOACs accounted for roughly 80% of all anticoagulants dispensed in Meuhedet (Figure 3). The growth rate of DOACs' use in Norway and England was significantly higher than in Israel (54% and 78%, respectively, Figures 4A,4B). No comparative data were available for Canada. In 2014, 82.1% of Meuhedet's naïve AF patients were eligible for DOACs treatment according to recommended clinical guidelines but did not meet the Israeli health basket criteria and initiated VKA treatment instead.

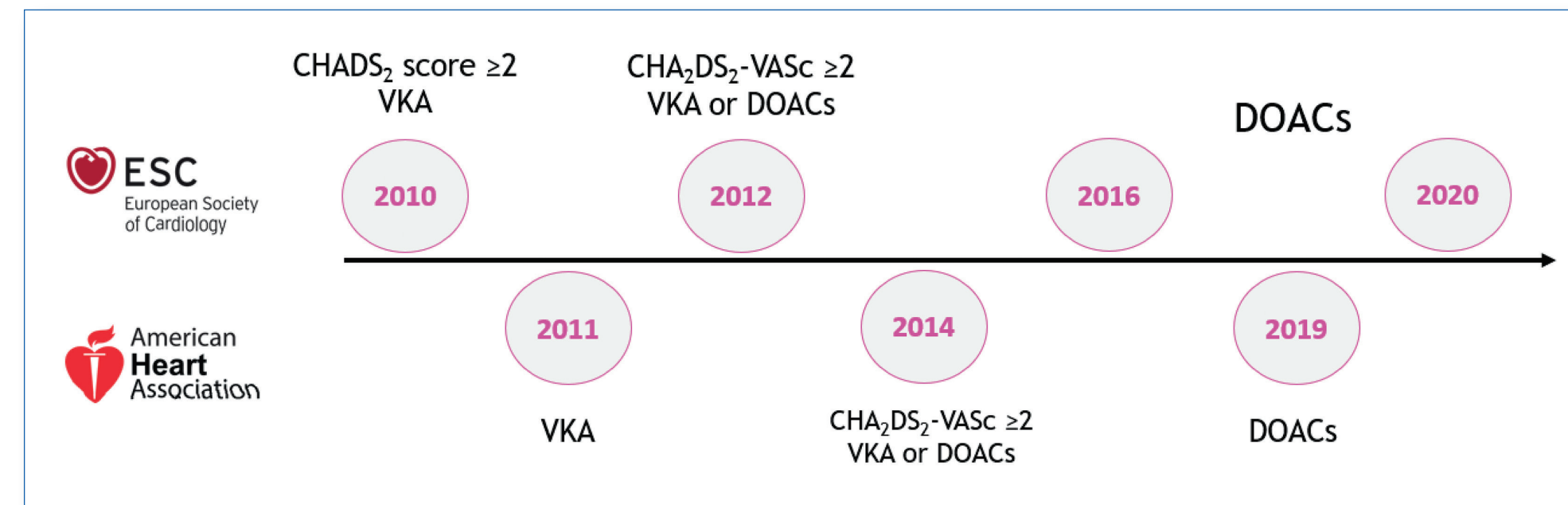


Figure 1: American Heart Association and European Society of Cardiology clinical guidelines evolution for anticoagulation in atrial fibrillation (AF). DOACs = direct oral anticoagulants, VKA = vitamin K antagonists.

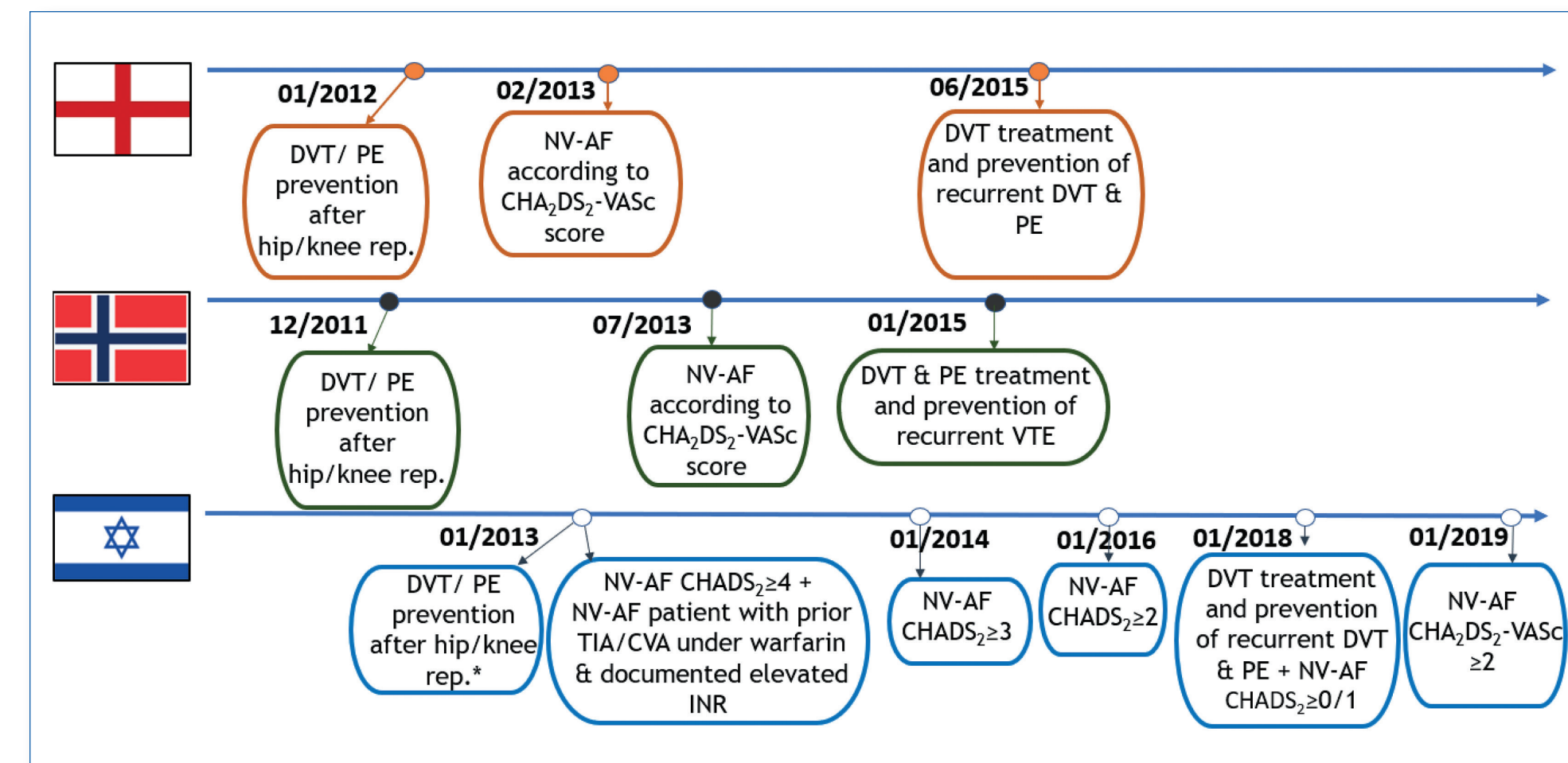


Figure 2: Apixaban's reimbursement timeline in England, Norway and Israel. * Note that dabigatran and rivaroxaban had already been approved in Israel for hip/knee rep. in 2010. DVT= Deep vein thrombosis, PE = pulmonary embolism, rep.= replacement, NV-AF = nonvalvular atrial fibrillation, TIA = transient ischemic attack, CVA = Cerebrovascular accident, INR = international normalized ratio.

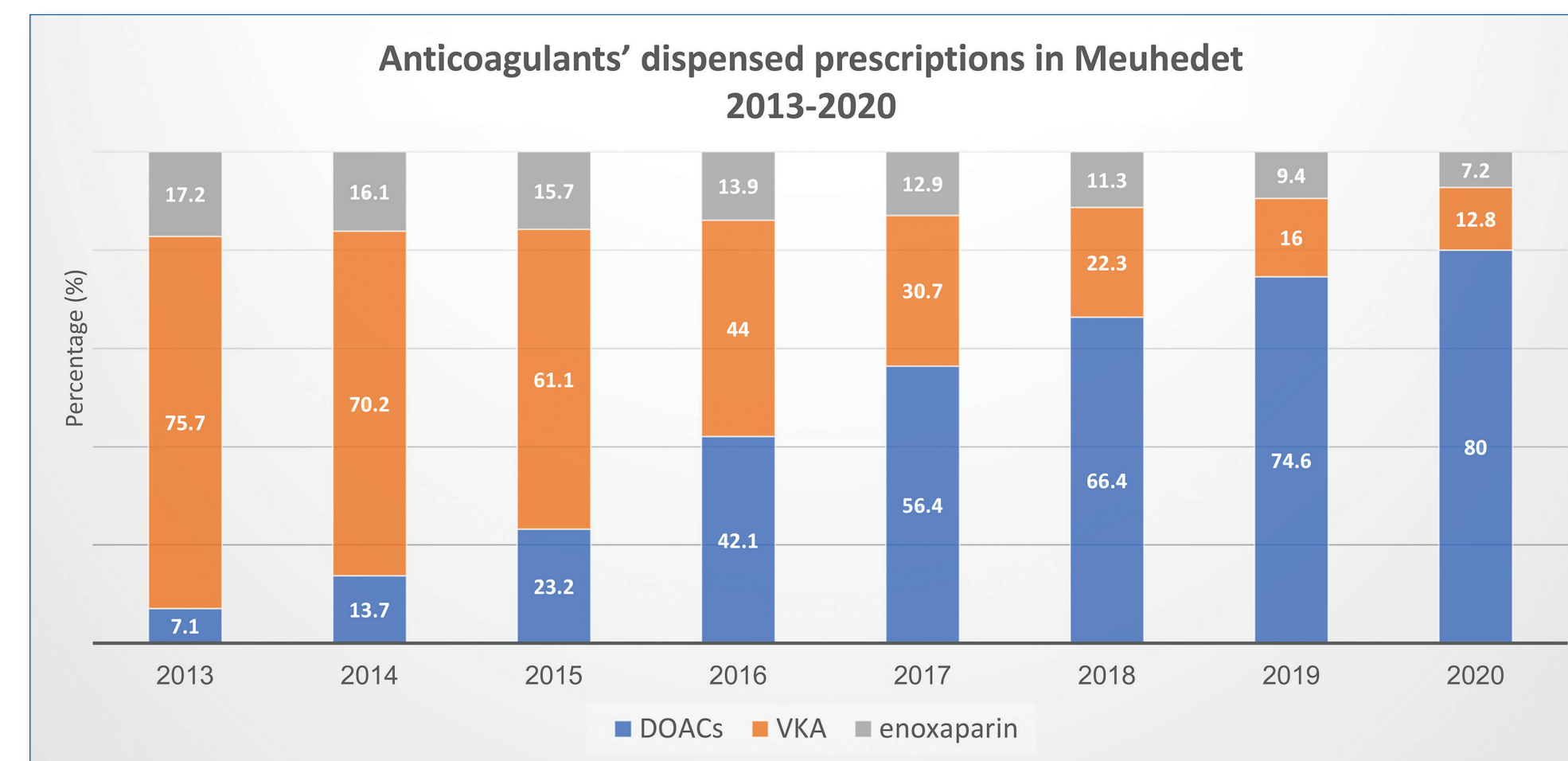


Figure 3: DOACs use as percentage of total dispensed anticoagulants' prescriptions in Meuhedet between 2013-2020. DOACs use gradually increased over the years on the expense of VKAs.

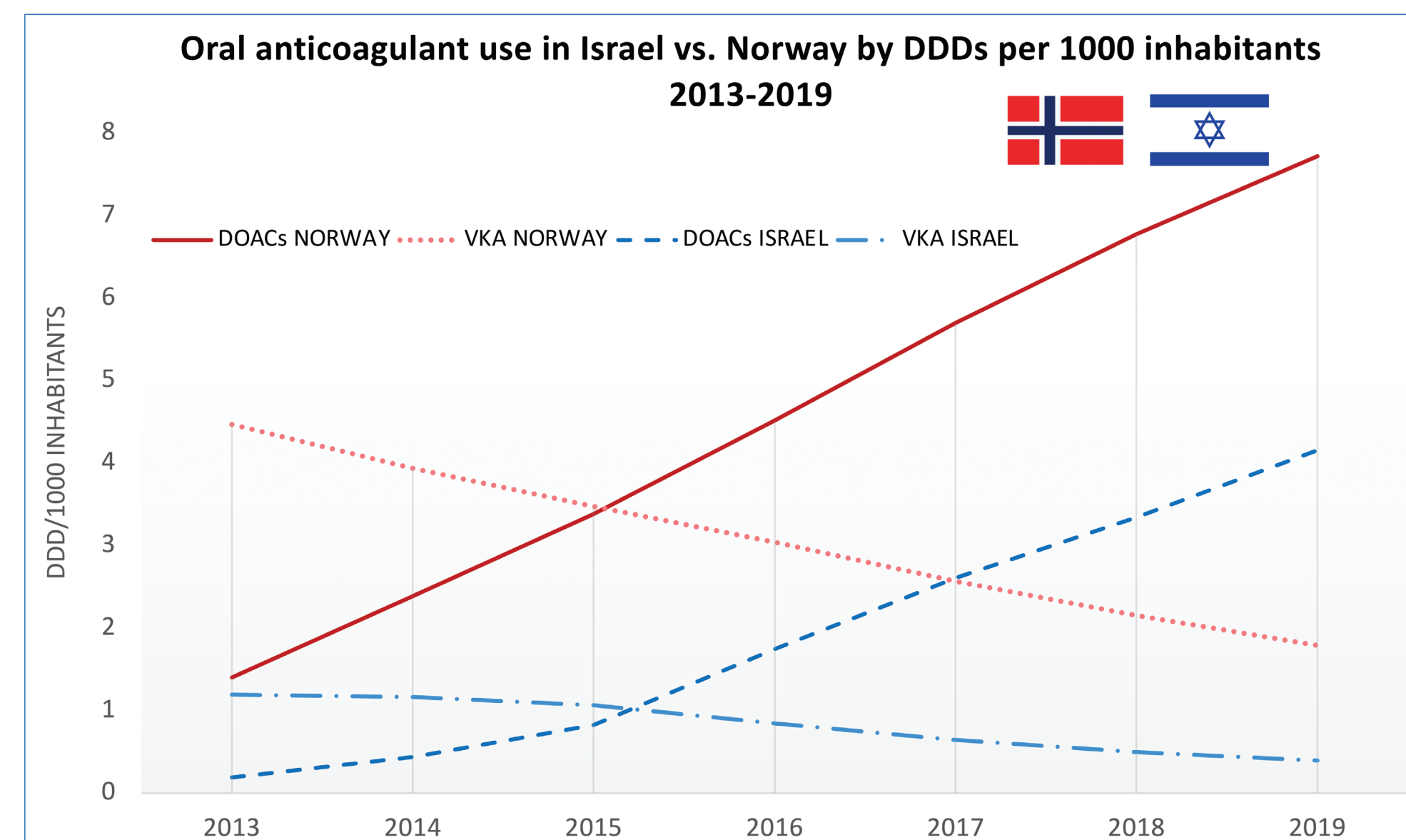


Figure 4A: Oral anticoagulant use in Israel vs. Norway by DDDs per 1000 inhabitants between 2013-2019. Drug consumption data in Norway was extracted from The Norwegian Prescription Database (NorPD), which includes information about prescription drugs issued in Norway since 2004.

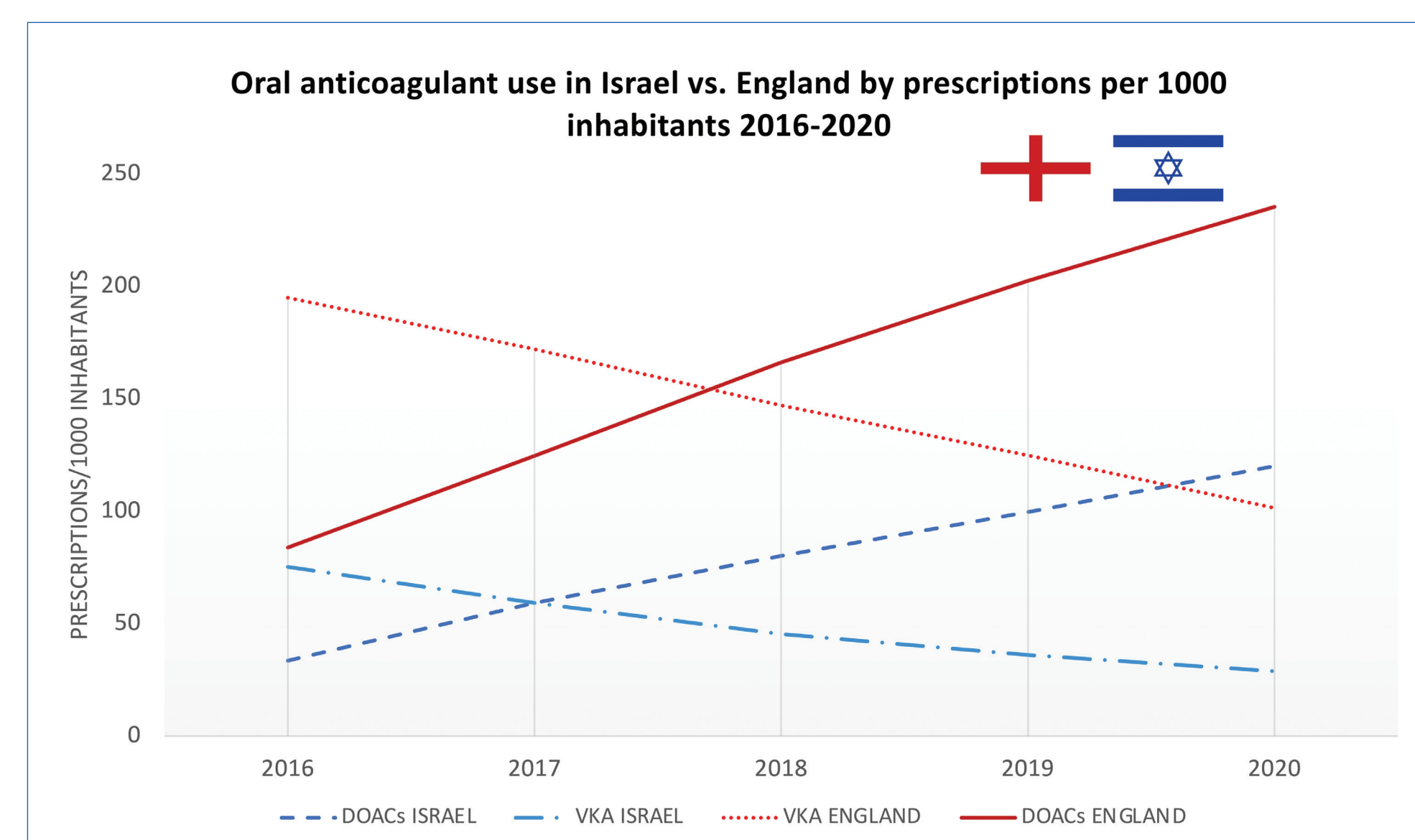


Figure 4B: Oral anticoagulant use in Israel vs. England by prescriptions per 1000 inhabitants between 2016-2020. Data on drug consumption in England was available from 2016 and was taken from the OpenPrescribing database.

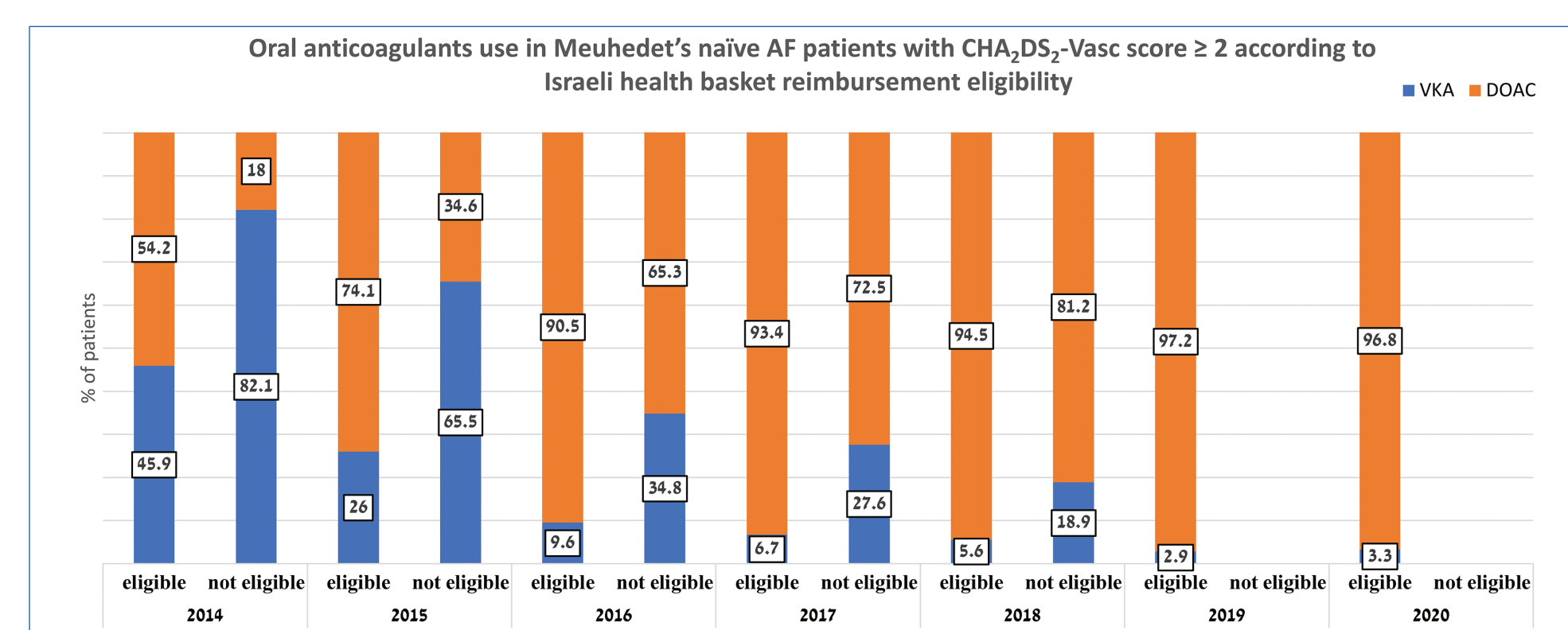


Figure 5: Oral anticoagulants use in Meuhedet's naïve AF patients with CHA₂DS₂-Vasc score ≥ 2 according to Israeli health basket reimbursement eligibility. There is a clear correlation between the timing of health basket's expansion for DOACs and the percentage of AF patients initiating treatment with these drugs.

This rate gradually declined over the years with the expansion of the health basket's eligibility criteria (Figure 5). DOACs' health basket eligibility status was found to be the strongest predictive variable for DOAC initiation over VKA (OR =12.1), followed by high socioeconomic status (OR=2.2) and advanced age (OR=1.45) (data not shown). DOACs were associated with significantly lower incidence of all-cause mortality compared with VKAs (HR = 0.54, 95% CI; 0.468–0.628, p<0.001) at 5.5 years follow up, but this effect later vanished. Meuhedet's expenditure on DOACs increased steadily over the study period and exceeded its cumulative health basket's budget (both adjusted to 2020 prices) as of 2020 (data not shown).

Limitations:

Our assumption according to which trends of anticoagulants' use derived from Meuhedet also apply to Israel needs to be examined, although qualitative data from other HMOs in Israel imply the same tendencies. Also, we analyzed DOACs' use as a group instead of specific molecules due to commercial confidentiality limitations of market share data.

Conclusions:

Although DOACs consumption has increased significantly over the years, its access under public funding in Israel did not meet recommended practice as in other western countries, probably due to budgetary restrictions of the Israeli government. Future controlled studies are needed to examine real life consequences (both clinical and economic) of these policy decisions at the Israeli national level.

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