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Research Article

Comparative Pharmacology of Direct Oral Anticoagulants and Vitamin K Antagonist

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ABSTRACT

Background: The prevalence of thrombus and use of anticoagulants is routine in clinical cardiology practice. Vitamin K antagonist (VKA) and/or Direct oral anticoagulants (DOAC) are used for resolution of the thrombus. Despite similar anticoagulation efficacy, use of DOAC is preferred due to their superior safety margin and reduced risk of bleeding. Currently the following DOAC are available for the prevention of thrombosis, i.e., dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. This study evaluates the comparative pharmacology of these DOAC and VKA to assess clinical preference. **Materials and Methods:** The human specific targets of DOAC and VKA (Warfarin) were identified from the SwissTargetPrediction server and analysed for their affinity. The targets were subclassified into functional categories and the relative proportion of each of the functional categories among the total number of targets was estimated. A novel concentration affinity (CA) ratio system was developed for the drugs to assess their safety margin and compared. **Results:** The following targets were identified has high affinity targets of DOAC or VKA i.e., coagulation factor X, hERG, matriptase, multidrug and toxin extrusion protein 1, plasminogen, quinone reductase 1 and 2, serine protease hepsin, solute carrier family 22 member 2 and thrombin. Apixaban and rivaroxaban were observed to have superior anticoagulation pharmacology compared to the other DOAC or VKA. Edoxaban and betrixaban were observed to have affinity against hERG, which carries the risk of prolonging QT interval and triggering ventricular tachyarrhythmia. **Conclusion:** This study shows the comparative pharmacology of DOAC and VKA and suggests preferential use of apixaban or rivaroxaban due to their superior pharmacodynamic effects and wider safety margin.

Keywords: Cardiovascular, Myocardial infarction, Thrombosis, Clot, Anticoagulant.

INTRODUCTION

The prevalence of thrombus especially in left ventricle significantly increases the risk of acute ischemic events.[1-3] This risk is further enhanced in presence of comorbidities such as diabetes, hypertension, recent incidence of myocardial infarction (MI) and several lifestyle factors negatively impacting health.[4-6] The incidence of left ventricle thrombus (LVT) is reported to range from 15 to 60% in patients post recovery from MI, while the incidence of LVT in general population without any comorbidities is not known, however it is assumed to be low (<5%).[1,2,5,7] The current approaches to managing incidence of LVT include use of Vitamin K antagonists (VKA) and/or Direct oral anticoagulants (DOAC) until resolution of the thrombus (~3 to 6 months).[1,5,7-9] Although recent clinical approaches show preferential use of DOAC over VKA, due to better patient compliance and drug safety issues (reduced bleeding and limited adverse drug interactions).[10-13] Currently the following five DOAC are available to be used for the prevention of thrombosis, i.e., dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. Several studies have compared the efficacy and safety of different anticoagulant approaches (i.e., DOAC, VKA and Heparin) to achieve resolution of thrombus under different clinical settings,[12-14] however such comparative efficacy between all the available DOAC with reference to their pharmacodynamic effects is lacking. Hence in this study comparative pharmacology of all five DOAC and VKA (warfarin) was assessed.

MATERIALS AND METHODS

The targets of DOAC (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) and VKA (Warfarin) were identified from the SwissTargetPrediction server as reported before[15,16] and analysed. Briefly, the isomeric SMILES sequence of the drugs obtained from the PubChem database were inputted into the SwissTargetPrediction server to identify the targets specific to homo sapiens. The target list for each of the drugs were processed based on their probability scores to identify highest affinity targets and compared. The targets without any probability score were excluded from the analysis. Drugs showing affinity with multiple targets were further analysed

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by subclassifying the targets into functional categories and the relative proportion of each of the functional categories among the total number of targets was estimated.

To assess the safety margin of the drugs, the plasma concentration (μM) of the drug achievable following different dose (low, mid and high dose) administration was estimated and the dose dependent concentration affinity ratio (CA ratio) for each of the drugs was calculated. The CA ratio is presented as mean ± SD of the values from low, mid and high dose. The affinity (μM) of the DOAC (to factor Xa/thrombin) and VKA (to Quinone reductase 1) was text mined from the literature. The volume of distribution (L) of the drugs reported in the DrugBank database was used for estimation of the plasma drug concentration (μM) achievable.[17,18] As the estimated concentration positively correlated with the plasma drug concentration (μM) reported in the literature, it was used for estimation of CA ratio, which reflects the safety margin of drug and the likeliness of significant off target effects when the CA ratio is high.

RESULTS

The following targets were identified has high affinity targets (probability score >0.8) of DOAC or VKA i.e., coagulation factor X, hERG, matriptase, multidrug and toxin extrusion protein 1, plasminogen, quinone reductase 1 and 2, serine protease hepsin, solute carrier family 22 member 2 and thrombin (Table 1). Although DOAC showed very high affinity (probability score >0.8) with at least one specific target, in contrast VKA (warfarin) was observed to have weak affinity to all its targets with the maximum affinity (probability score: 0.13) observed for Quinone reductase 1 (Table 1). Among the DOAC, dabigatran was observed to have high affinity (probability score >0.8) for maximum number of targets (coagulation factor X, multidrug/toxin extrusion protein 1, plasminogen, serine protease hepsin, solute carrier family 22 member 2 and thrombin) (Table 1).

Based on the analysis profile observed in this study it appears that apixaban has the superior anticoagulation pharmacology compared to the other DOAC or VKA. The superiority of apixaban is due to its specific high affinity to selective targets (coagulation factor X and thrombin) involved in the coagulation cascade and its low affinity (probability score: <0.2) to off targets (Tables 1 to 4). Besides apixaban, rivaroxaban also showed high affinity to coagulation factor X and matriptase but it had a lower

Table 1: Comparative pharmacology of direct oral anticoagulants and antiplatelet agent against their major targets. Values indicate the probability interaction score of drug with its target.

Major Targets	Warfarin	Rivaroxaban	Apixaban	Dabigatran	Edoxaban	Betrixaban
Coagulation Factor X		0.99	0.96	0.99	1	1
hERG					0.13	1
Matriptase		0.99				
Multidrug and toxin extrusion protein 1				0.99		
Plasminogen				0.99		
Quinone reductase 1	0.13					
Quinone reductase 2				0.33		
Serine protease hepsin				0.99		
Solute carrier family 22 member 2				0.99		
Thrombin		0.10	0.96	0.99	0.13	

Table 2: All the potential targets of warfarin in humans.

Target	Uniprot ID	Target Class	Probability*
CYP2C9	P11712	Cytochrome P450	0.1
CDK9 CCNT1	P50750 O60563	Cytosolic protein	0.1
NQO1	P15559	Enzyme	0.13
HMOX1	P09601	Enzyme	0.1
ASAH1	Q13510	Enzyme	0.1
NOS2	P35228	Enzyme	0.1
PYGL	P06737	Enzyme	0.1
PARP1	P09874	Enzyme	0.1
PIK3CA PIK3R1	P42336 P27986	Enzyme	0.1
AOC3	Q16853	Enzyme	0.1
ALPL	P05186	Enzyme	0.1
AKR1B1	P15121	Enzyme	0.1
PARP3	Q9Y6F1	Enzyme	0.1
PIK3CB	P42338	Enzyme	0.1
PIK3CD	O00329	Enzyme	0.1
TNKS2	Q9H2K2	Enzyme	0.1
PFKFB4 PFKFB3	Q16877 Q16875	Enzyme	0.1
LDHA	P00338	Enzyme	0.1
ALDH3A1	P30838	Enzyme	0.1
MIF	P14174	Enzyme	0.1
HSD17B3	P37058	Enzyme	0.1
SIRT2	Q8IXJ6	Eraser	0.1
KDM5C	P41229	Eraser	0.1
KDM4B	O94953	Eraser	0.1
KDM5B	Q9UGL1	Eraser	0.1
KDM4A	O75164	Eraser	0.1
CHRM5	P08912	Family A GPCR	0.1
ADORA2B	P29275	Family A GPCR	0.1
ADORA3	P0DMS8	Family A GPCR	0.1
CCKBR	P32239	Family A GPCR	0.1
CNR2	P34972	Family A GPCR	0.1
CNR1	P21554	Family A GPCR	0.1
DRD4	P21917	Family A GPCR	0.1
TACR1	P25103	Family A GPCR	0.1
CHRM1	P11229	Family A GPCR	0.1
CHRM3	P20309	Family A GPCR	0.1
ADORA2A	P29274	Family A GPCR	0.1
CHRM2	P08172	Family A GPCR	0.1
CHRM4	P08173	Family A GPCR	0.1
GPR55	Q9Y2T6	Family A GPCR	0.1
GPR35	Q9HC97	Family A GPCR	0.1
GPR18	Q14330	Family A GPCR	0.1
PLCG2	P16885	Hydrolase	0.1
MALT1	Q9UDY8	Hydrolase	0.1
CFTR	P13569	Ion channel	0.1
LRRK2	Q5S007	Kinase	0.1
IRAK4	Q9NWZ3	Kinase	0.1
MAPK1	P28482	Kinase	0.1
SRC	P12931	Kinase	0.1

continued...

Table 2: Cont'd.

Target	Uniprot ID	Target Class	Probability*
GSK3B	P49841	Kinase	0.1
PRKDC	P78527	Kinase	0.1
PLK1	P53350	Kinase	0.1
MAPK9	P45984	Kinase	0.1
JAK1	P23458	Kinase	0.1
MKNK1	Q9BUB5	Kinase	0.1
CDK2	P24941	Kinase	0.1
GRK2	P25098	Kinase	0.1
TYK2	P29597	Kinase	0.1
PIM1	P11309	Kinase	0.1
IGF1R	P08069	Kinase	0.1
FLT3	P36888	Kinase	0.1
CHEK1	O14757	Kinase	0.1
MAPK8	P45983	Kinase	0.1
MYLK	Q15746	Kinase	0.1
EIF2AK3	Q9NZJ5	Kinase	0.1
EGFR	P00533	Kinase	0.1
FGFR1	P11362	Kinase	0.1
CLK4	Q9HAZ1	Kinase	0.1
AKT1	P31749	Kinase	0.1
CDC7	O00311	Kinase	0.1
JAK2	O60674	Kinase	0.1
KDR	P35968	Kinase	0.1
PLK3	Q9H4B4	Kinase	0.1
CA9	Q16790	Lyase	0.1
ITGB7 ITGA4	P26010 P13612	Membrane receptor	0.1
PTGS2	P35354	Oxidoreductase	0.1
IMPDH2	P12268	Oxidoreductase	0.1
PTGS1	P23219	Oxidoreductase	0.1
CDC25A	P30304	Phosphatase	0.1
CDC25B	P30305	Phosphatase	0.1
CDC25C	P30307	Phosphatase	0.1
PDE9A	O76083	Phosphodiesterase	0.1
PDE1C	Q14123	Phosphodiesterase	0.1
CASP3	P42574	Protease	0.1
CASP1	P29466	Protease	0.1
CASP7	P55210	Protease	0.1
BACE1	P56817	Protease	0.1
EPHX2	P34913	Protease	0.1
MMP13	P45452	Protease	0.1
METAP2	P50579	Protease	0.1
PCSK7	Q16549	Protease	0.1
SHBG	P04278	Secreted protein	0.1
WNT3A	P56704	Unclassified protein	0.1
TNNC1 TNNT2	P63316 P45379	Unclassified protein	0.1
BCL2A1	Q16548	Unclassified protein	0.1
KMT5A	Q9NQR1	Writer	0.1

*Values indicate the probability interaction score of drug with its target, with value of 1 indicating significant interaction while value of 0.1 indicates weaker interaction.

affinity (probability score: 0.10) to thrombin. However unlike apixaban, rivaroxaban showed highly selective and specific pharmacology against proteases (Table 3, Figure 1). Edoxaban and betrixaban also showed selective high affinity (probability score: >0.8) towards coagulation factor X, however both these DOAC were observed to have affinity against hERG (Table 1), which carries the risk of prolonging QT interval and triggering ventricular tachyarrhythmia.

Table 3: All the potential targets of rivaroxaban in humans.

Target	Uniprot ID	Target Class	Probability*
F10	P00742	Protease	0.99
ST14	Q9Y5Y6	Protease	0.99
F2	P00734	Protease	0.10

*Values indicate the probability interaction score of drug with its target, with value of 1 indicating significant interaction while value of 0.1 indicates weaker interaction.

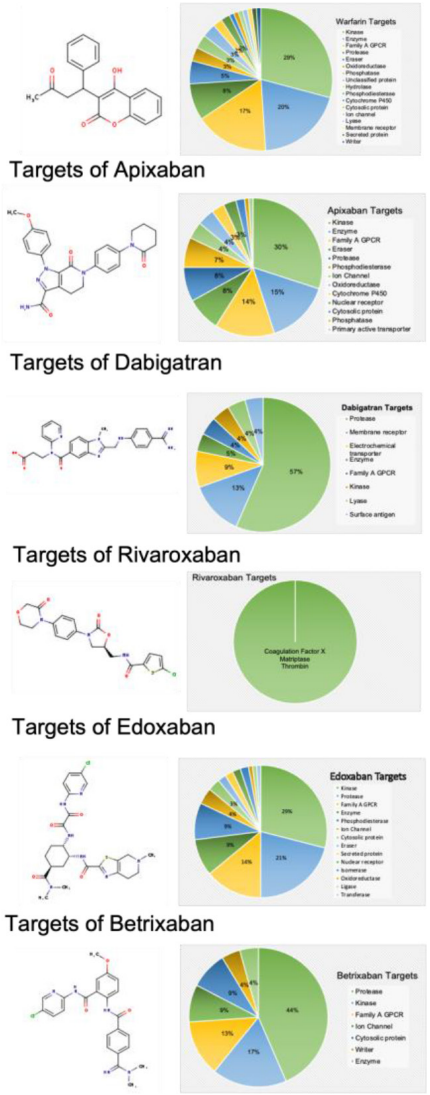

Figure 1: All the potential targets of warfarin, apixaban, dabigatran, rivaroxaban, edoxaban, and betrixaban in humans grouped based on functional categories. The target functional category which showed probability of interaction with the drug are expressed as the percent of the total pool of targets.

Table 4: All the potential targets of apixaban in humans.

Target	Uniprot ID	Target Class	Probability*
TBXAS1	P24557	Cytochrome P450	0.12
CYP3A4	P08684	Cytochrome P450	0.12
CYP19A1	P11511	Cytochrome P450	0.12
ALOX5AP	P20292	Cytosolic protein	0.12
CCNE2 CDK2 CCNE1	O96020 P24941	Cytosolic protein	0.12
PIK3CA	P42336	Enzyme	0.12
PFKFB3	Q16875	Enzyme	0.12
PIK3CD	O00329+C9:C10	Enzyme	0.12
DUT	P33316	Enzyme	0.12
PIK3CB	P42338	Enzyme	0.12
PIK3CG	P48736	Enzyme	0.12
MGAT2	Q10469	Enzyme	0.12
DGAT2	Q96PD7	Enzyme	0.12
PORCN	Q9H237	Enzyme	0.12
IDO1	P14902	Enzyme	0.12
GCK	P35557	Enzyme	0.12
DCK	P27707	Enzyme	0.12
QPCT	Q16769	Enzyme	0.12
SCD	O00767	Enzyme	0.12
SOAT1	P35610	Enzyme	0.12
SIRT2	Q8IXJ6	Eraser	0.12
SIRT1	Q96EB6	Eraser	0.12
SIRT3	Q9NTG7	Eraser	0.12
HDAC1	Q13547	Eraser	0.12
HDAC3	O15379	Eraser	0.12
HDAC2	Q92769	Eraser	0.12
HDAC11	Q96DB2	Eraser	0.12
HDAC10	Q969S8	Eraser	0.12
ADORA1	P30542	Family A GPCR	0.12
ADORA2A	P29274	Family A GPCR	0.12
CNR1	P21554	Family A GPCR	0.12
DRD2	P14416	Family A GPCR	0.12
DRD3	P35462	Family A GPCR	0.12
PTAFR	P25105	Family A GPCR	0.12
FPR2	P25090	Family A GPCR	0.12
GNRHR	P30968	Family A GPCR	0.12
GPR39	O43194	Family A GPCR	0.12
CNR2	P34972	Family A GPCR	0.12
ADORA2B	P29275	Family A GPCR	0.12
CALCRL	Q16602	Family A GPCR	0.12
CRHR1	P34998	Family A GPCR	0.12
GRM2	Q14416	Family A GPCR	0.12
SLC8A1	P32418	Ion Channel	0.12
GABRA2 GABRB3	P47869 P28472	Ion channel	0.12
KCNK9	Q9NPC2	Ion channel	0.12
KCNK3	O14649	Ion channel	0.12
TXK	P42681	Kinase	0.12
TGFBR1	P36897	Kinase	0.12
MAPK1	P28482	Kinase	0.12
IRAK4	Q9NWZ3	Kinase	0.12
MAPK8	P45983	Kinase	0.12
ROCK1	Q13464	Kinase	0.12
PTK2	Q05397	Kinase	0.12
PDGFRA PDGFRB	P16234 P09619	Kinase	0.12
CSNK1D	P48730	Kinase	0.12
IKBKE	Q14164	Kinase	0.12
TBK1	Q9UHD2	Kinase	0.12
MAPK11	Q15759	Kinase	0.12
FLT4	P35916	Kinase	0.12
CDK5R1 CDK5	Q15078 Q00535	Kinase	0.12
TNIK	Q9UKE5	Kinase	0.12
CHUK	O15111	Kinase	0.12
RPS6KA3	P51812	Kinase	0.12
WEE1	P30291	Kinase	0.12
CCND1 CDK4	P24385 P11802	Kinase	0.12
MAP4K4	O95819	Kinase	0.12
PRKD1	Q15139	Kinase	0.12
TNK2	Q07912	Kinase	0.12
CSNK2A1	P68400	Kinase	0.12
CSNK2A2	P19784	Kinase	0.12
ZAP70	P43403	Kinase	0.12
DDR1	Q08345	Kinase	0.12
MAPK10	P53779	Kinase	0.12
GSK3A	P49840	Kinase	0.12
MAPK9	P45984	Kinase	0.12
AKT1	P31749	Kinase	0.12
THRB	P10828	Nuclear receptor	0.12
NR5A1	Q13285	Nuclear receptor	0.12
PPARG	P37231	Nuclear receptor	0.12
DHODH	Q02127	Oxidoreductase	0.12
MAOB	P27338	Oxidoreductase	0.12
IMPDH2	P12268	Oxidoreductase	0.12
ALOX5	P09917	Oxidoreductase	0.12
CDC25A	P30304	Phosphatase	0.12
PDE7A	Q13946	Phosphodiesterase	0.12
PDE4A	P27815	Phosphodiesterase	0.12
PDE5A	O76074	Phosphodiesterase	0.12
PDE9A	O76083	Phosphodiesterase	0.12
PDE3A	Q14432	Phosphodiesterase	0.12
PDE4D	Q08499	Phosphodiesterase	0.12
PDE1B	Q01064	Phosphodiesterase	0.12
ABCG2	Q9UNQ0	Active transporter	0.12
F2	P00734	Protease	0.96
F10	P00742	Protease	0.96
LGMN	Q99538	Protease	0.12
CFD	P00746	Protease	0.12
BACE1	P56817	Protease	0.12
ADAMTS5	Q9UNA0	Protease	0.12
MMP9	P14780	Protease	0.12
PSEN2 PSENEN	P49810 Q9NZ42	Protease	0.12

*Values indicate the probability interaction score of drug with its target, with value of 1 indicating significant interaction while value of 0.1 indicates weaker interaction.

This study also analysed the target functional categories of each of the anticoagulants, which are summarized in Figure 1. The major target categories of warfarin were kinase (29%), enzyme (20%) and family A GPCR (17%) collectively accounting for over 50% of the targets, although the affinity for all these targets was low (probability score < 0.20) (Table 2). Similar to warfarin the major target categories of apixaban were also kinase (30%), enzyme (15%) and family A GPCR (14%) (Figure 1) all of which showed lower affinity interaction (Table 4). About 8% of apixaban targets were protease among which it had highest affinity (probability score: >0.8) for coagulation factor II (thrombin) and X. The major target categories of dabigatran were protease (57%) and membrane receptors (13%) (Figure 1). Among these targets dabigatran showed high affinity interactions with several proteases and two electrochemical transporters (Table 5). Dabigatran was also observed to target quinone reductase 2 with moderate affinity and this is likely to lead to synergistic pharmacological effects with warfarin (which targets quinone reductase 1). Rivaroxaban selectively targeted proteases and was the only DOAC observed to have minimal number of off targets (Figure 1 and Table 3). The major target categories of edoxaban were kinase (29%), protease (21%) and family A GPCR (14%), while low affinity interactions with several off targets including hERG channels was also observed (Figure 1 and Table 6). The major target categories of betrixaban were protease (44%), kinase (17%) and family A GPCR (13%) (Figure 1). Betrixaban showed high affinity interaction with coagulation factor X and hERG channels (Table 7).

Table 5: All the potential targets of dabigatran in humans.

Target	Uniprot ID	Target Class	Probability*
SLC22A2	O15244	Electrochemical transporter	0.99
SLC47A1	Q96FL8	Electrochemical transporter	0.99
PLG	P00747	Protease	0.99
F2	P00734	Protease	0.99
HPN	P05981	Protease	0.99
F10	P00742	Protease	0.99
NQO2	P16083	Enzyme	0.33
TMPRSS15	P98073	Protease	0.11
ITGAV ITGB1	P06756	Membrane receptor	0.11
F3 F7	P13726	Protease	0.11
RPS6KA3	P51812	Kinase	0.11
C3AR1	Q16581	Family A GPCR	0.11
CA12	O43570	Lyase	0.11
ITGA2B	P08514	Membrane	0.11
PRSS3	P35030	Protease	0.11
C1S	P09871	Protease	0.11
TMPRSS11D	O60235	Protease	0.11
ITGA4	P13612	Membrane receptor	0.11
F3	P13726	Surface antigen	0.11
PROC	P04070	Protease	0.11
MMP12	P39900	Protease	0.11
MMP8	P22894	Protease	0.11
MMP2	P08253	Protease	0.11

*Values indicate the probability interaction score of drug with its target, with value of 1 indicating significant interaction while value of 0.1 indicates weaker interaction.

Table 6: All the potential targets of edoxaban in humans.

Target	Uniprot ID	Target Class	Probability*
PIK3CA	P42336	Enzyme	0.13
PARP10	Q53GL7	Enzyme	0.13
PARP1	P09874	Enzyme	0.13
HSD11B1	P28845	Enzyme	0.13
TNKS2	Q9H2K2	Enzyme	0.13
TNKS	O95271	Enzyme	0.13
PARP6	Q2NL67	Enzyme	0.13
PARP3	Q9Y6F1	Enzyme	0.13
PARP2	Q9UGN5	Enzyme	0.13
HDAC2	Q92769	Eraser	0.13
HDAC8	Q9BY41	Eraser	0.13
CCKBR	P32239	Family A GPCR	0.13
ADORA1	P30542	Family A GPCR	0.13
ADORA2A	P29274	Family A GPCR	0.13
P2RY12	Q9H244	Family A GPCR	0.13
TACR3	P29371	Family A GPCR	0.13
AVPR1A	P37288	Family A GPCR	0.13
HCRTR2	O43614	Family A GPCR	0.13
HCRTR1	O43613	Family A GPCR	0.13
OXTR	P30559	Family A GPCR	0.13
NPY5R	Q15761	Family A GPCR	0.13
CHRM2	P08172	Family A GPCR	0.13
CHRM1	P11229	Family A GPCR	0.13
CHRM3	P20309	Family A GPCR	0.13
ADORA3	P0DMS8	Family A GPCR	0.13
PPIA	P62937	Isomerase	0.13
FKBP1A	P62942	Isomerase	0.13
MTOR	P42345	Kinase	0.13
PDPK1	O15530	Kinase	0.13
GSK3B	P49841	Kinase	0.13
NTRK1	P04629	Kinase	0.13
AKT1	P31749	Kinase	0.13
MARK1	Q9P0L2	Kinase	0.13
MAPK3	P27361	Kinase	0.13
CCND1 CDK4	P24385 P11802	Kinase	0.13
ITK	Q08881	Kinase	0.13
EGFR	P00533	Kinase	0.13
PTK2	Q05397	Kinase	0.13
AURKB	Q96GD4	Kinase	0.13
RPS6KA3	P51812	Kinase	0.13
ROCK1	Q13464	Kinase	0.13
MAP2K1	Q02750	Kinase	0.13
GRK1	Q15835	Kinase	0.13
GRK5	P34947	Kinase	0.13
CDK5R1 CDK5	Q15078 Q00535	Kinase	0.13

continue...

Table 6: Cont'd.

Target	Uniprot ID	Target Class	Probability*
SYK	P43405	Kinase	0.13
SRC	P12931	Kinase	0.13
MET	P08581	Kinase	0.13
MAPK14	Q16539	Kinase	0.13
IGF1R	P08069	Kinase	0.13
MAPK8	P45983	Kinase	0.13
JAK3	P52333	Kinase	0.13
FLT3	P36888	Kinase	0.13
CCNA2 CDK2	P20248 P24941	Kinase	0.13
MAPK1	P28482	Kinase	0.13
BRAF	P15056	Kinase	0.13
ACACB	O00763	Ligase	0.13
ESR1	P03372	Nuclear receptor	0.13
NR3C1	P04150	Nuclear receptor	0.13
CDK1 CCNB1	P06493 P14635	Other cytosolic protein	0.13
CDK7 CCNH	P50613 P51946	Other cytosolic protein	0.13
CDK9 CCNT1	P50750 O60563	Other cytosolic protein	0.13
CFTR	P13569	Other ion channel	0.13
PTGS2	P35354	Oxidoreductase	0.13
PDE5A	O76074	Phosphodiesterase	0.13
PDE2A	O00408	Phosphodiesterase	0.13
PDE4A	P27815	Phosphodiesterase	0.13
PDE11A	Q9HCR9	Phosphodiesterase	0.13
PDE7A	Q13946	Phosphodiesterase	0.13
PDE1A	P54750	Phosphodiesterase	0.13
PDE9A	O76083	Phosphodiesterase	0.13
PDE6C	P51160	Phosphodiesterase	0.13
PDE4D	Q08499	Phosphodiesterase	0.13
ABCC5	O15440	Active transporter	0.13
ABCB1	P08183	Active transporter	0.13
F10	P00742	Protease	1.00
F2	P00734	Protease	0.13
MMP2	P08253	Protease	0.13
PLAT	P00750	Protease	0.13
KLKB1	P03952	Protease	0.13
CAPN1	P07384	Protease	0.13
CTSB	P07858	Protease	0.13
CAPN2	P17655	Protease	0.13
CFD	P00746	Protease	0.13
ELANE	P08246	Protease	0.13
MMP3	P08254	Protease	0.13
MMP9	P14780	Protease	0.13
MMP8	P22894	Protease	0.13
CTSD	P07339	Protease	0.13
CTSK	P43235	Protease	0.13
CAPN1 CAPNS1	P07384 P04632	Protease	0.13
CTSS	P25774	Protease	0.13
CTSV	O60911	Protease	0.13
PSMB2	P49721	Protease	0.13
CTSL	P07711	Protease	0.13
REN	P00797	Protease	0.13
TNF	P01375	Secreted protein	0.13
TUBB1	Q9H4B7	Structural protein	0.13
SGMS1	Q86VZ5	Transferase	0.13
KCNH2	Q12809	Ion channel	0.13

continue...

*Values indicate the probability interaction score of drug with its target, with value of 1 indicating significant interaction while value of 0.1 indicates weaker interaction.

Table 7: All the potential targets of betrixaban in humans.

Target	Uniprot ID	Target Class	Probability*
QPCT	Q16769	Enzyme	0.1
PTGIR	P43119	Family A GPCR	0.1
BDKRB1	P46663	Family A GPCR	0.1
GRM5	P41594	Family A GPCR	0.1
EIF2AK2	P19525	Kinase	0.1
EIF2AK1	Q9BQI3	Kinase	0.1
PDK1	Q15118	Kinase	0.1
CCND1 CDK4	P24385 P11802	Kinase	0.1
CCNE2 CDK2 CCNE1	O96020 P24941	Cytosolic protein	0.1
HSP90AA1	P07900	Cytosolic protein	0.1
F10	P00742	Protease	1.0
KLKB1	P03952	Protease	0.1
F9	P00740	Protease	0.1
PROC	P04070	Protease	0.1
TMPRSS6	Q8IU80	Protease	0.1
REN	P00797	Protease	0.1
MMP3	P08254	Protease	0.1
MMP9	P14780	Protease	0.1
MMP1	P03956	Protease	0.1
ADAM17	P78536	Protease	0.1
KCNH2	Q12809	Ion channel	1.0
SCN9A	Q15858	Ion channel	0.1
DNMT1	P26358	Writer	0.1

*Values indicate the probability interaction score of drug with its target, with value of 1 indicating significant interaction while value of 0.1 indicates weaker interaction.

To assess the likeliness of off target effect, in this study CA ratio was developed. CA ratio estimates the threshold by which the plasma concentration of the drug is higher than the affinity of the drug to its primary target. Hence drugs with higher CA ratio are highly likely to interact with off targets and produce undesired pharmacodynamics. The CA ratio of warfarin was significantly higher than any of the DOAC (Figure 2). Among the DOAC, apixaban had the highest CA ratio especially at higher drug dose, while apixaban, rivaroxaban, dabigatran and edoxaban showed similar CA ratio for low and medium dose range (Figure 2). Betrixaban showed the least CA ratio among the DOAC (Figure 2), indicting it being least likely to interact with off target effects. However the high affinity of betrixaban to hERG channels is of concern as highlighted above.

DISCUSSION

In this analysis apixaban and rivaroxaban were observed to have optimal pharmacological profile for achieving anticoagulation effect.

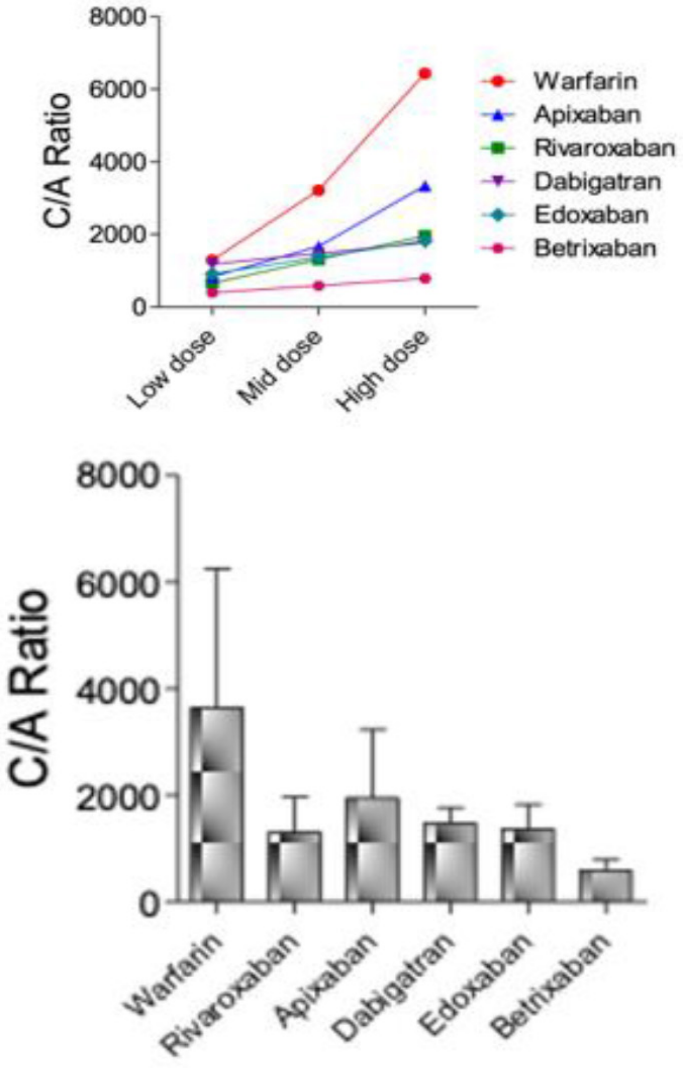

Figure 2: Dose dependent concentration affinity (C/A) ratio of warfarin, apixaban, rivaroxaban, dabigatran, edoxaban, and betrixaban in humans. The bar graphs represents the average C/A ratio. Data is represented as mean ± SD of the C/A ratio values estimated from low, mid and high dose of each of the drugs.

It is also reasonable to conclude that apixaban will have a superior pharmacodynamic outcome compared to rivaroxaban despite its specificity and lower number of off target effects due to the higher affinity of apixaban against factor X and thrombin. These observation are consistent with reports concluding from clinical efficacy trials.[11,12,14] Moreover rivaroxaban was observed to off target matriptase with high affinity, which is likely to induce iron deficiency anaemia in patients on chronic use[19,20] and this is likely to further increase the risk of bleeding. Although apixaban had several off targets, all of these were low affinity interactions, which is least likely to trigger undesired pharmacodynamic effects as long the low to medium range dosage is adhered to and adequate chrono-pharmacological measures[21] are taken to avoid drug accumulation over its chronic use. The specific higher affinity interactions of apixaban with factor X and thrombin will account for its superior anticoagulation pharmacology. Further the CA ratio of apixaban at low to medium dose range (2 to 5 mg/day) was similar to other DOAC, which together with its low affinity to off targets makes it the DOAC of choice for clinical use over a longer term (greater than 3 months). Considering the selectivity of rivaroxaban to proteases, significantly smaller number of off targets and a lower CA ratio across winder dose range (10 to 30 mg/day), the clinical use of rivaroxaban can be preferred for short term (less than 4 weeks). However any long term use of rivaroxaban will require continuous monitoring of haemoglobin (Hb) levels and anaemic status of the patient.

Unlike apixaban or rivaroxaban, dabigatran showed higher affinity to several off targets including quinone reductase 2. Hence dabigatran is likely to show significant undesired pharmacodynamic outcome, including potentiation of warfarin effects.[22] Hence based on the observations from this study the combined use of dabigatran and warfarin should be avoided. The CA ratio of dabigatran was comparable to apixaban and rivaroxaban, hence these DOAC should be prefered over the use of dabigatran. This conclusion is consistent with studies directly comparing these DOAC under clinical setting.[5,10-14] While edoxaban and betrixaban showed higher affinity to factor X compared to apixaban, both these drugs had several undesirable off targets including the hERG channels. Considering the significantly higher risk of ventricular tachyarrhythmia due to QT prolongation induced by hERG channels, in the opinion of this study use of edoxaban and betrixaban for anticoagulation effects should be avoided.

Several studies have previously reported the superiority of DOAC compared to VKA (warfarin)[12,14,23,24] and this was further evident from the observations in this study. Warfarin showed low affinity interaction with several off targets including its major target (quinone reductase 1) responsible to achieve anticoagulation effects. Further warfarin showed significantly higher CA ratio compared to the DOAC, which increase the likeliness of the warfarin's off target pharmacodynamics. This observation further supports the wider literature expressing concerns on the relative safety margin of warfarin use.[25-27] Clinically warfarin is also used in combination with DOAC and based on this study it is recommended that only apixaban or rivaroxaban is considered to be used with warfarin when necessary. As mentioned above the use of warfarin with dabigatran should be avoided as this is likely to be associated with higher risk of bleeding and several undesired pharmacodynamic effects.

In summary this study shows the comparative pharmacology of DOAC and VKA and suggests preferential use of apixaban or rivaroxaban due to their superior pharmacodynamic effects and wider safety margin.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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