



5HVHDFK \$UWLFOH 20,&6 ,QWH

DVDNODQL#KRWPDLO FRP

5HFHLYHG 6CHSWHH PEHU \$ F6HHSWHHQ EGDUWH 3XE@HSDWHPHQ LGDWH
&RS\ULJKW < .XQGDJXOZDU *. 7KLV LV DQ RSHQ DFFHVV DUWLFOH GLVWULEXWHG XQGHU WKH WHUPV
XVH GLVWULEXWLRQ DQG UHSURGXFWLRQ LQ DQ\ PHGLXP SURYLGHG WKH RULJLQDO DXWKRU DQG VRXU

\$EVWUDFW

&RORUHFWDO LV WKH WKLUG PRVW FRPPRQ FDQFHU LQ PHQ 7RWDO PHVUHFWDO
WUHDWPHQW IRU UHFWDO FDQFHU ZLWK FKHPHUDGLRWKHUHS\ SUHFHGLQJ WKH
PDOLJQDQFLHV /DWHUDO SHOYLF O\PSK QRGH GLVVHFWLRQ /3/1' DOWKRXJK D S
WUHDWPHQW LQ -DSDQ KDV QRW EHHQ DGRSWHG E\ VXUJHRQV LQ WKH UHVV RI WH
RQ ZKHWKHU ODWHUDO SHOYLF QRGH PHWDVWDV LV UHSUHVHQWV ORFDOLJHG RU P
FRQVLGHU ODWHUDO SHOYLF QRGHV DV UHJLRQDO GLVHDVH DQG KHQFH SHUIRU
VWDJH 7 RU PRUH RU ZLWK LQYROYHG PHVUHFWDO QRGHV ,Q FRQWUDVW VWD

,QWURGXFWRQ

&RORUHFWDO FDQFHU LV WKH WKLUG PRVW FRPPRQ FDQFHU LQ PHQ >
GLVHDVH DQG KHQFH SHUIR DQVOLJDPHQW \$OWKRXJK WKH VXEMHFW R
JHQHUDOO\ FRQVLGHUHG WR EH D SDUW PH V
HDVW DQG WKH ZHVW PD\ EH VLPLODU EXW WKH PDQDJHPPHQW RI /3/1
FRPSO@WHQV WKH ZHVW 1\$&757 LV PRUH FRPPRQO\ XVHG
Z

KLFK LV DOVR VHHQ LQ ,QGLD ZKHUHDV
XSIURQW VXUJHU\ > @ ,QFLGHQFH YDULHV
VLJH RI WKH WXPUR SDWKRORJLFDO 7 VW
DQG JUDGLMURHQDOV SURQ
> @QYROYHPPHQW RI WKH ODWHUDO SHOY

PHVHQWHULF QRGHV KDV EHHQ GRFXPHQWEDWCHKO SRWB DWHSDVLEBOWYLF QRGDO U
WKH GLVWDQFH IURP WKH DQDO YHUJH RGMVULHUV H3/1' WEDWHLQREBSUMKURID VDWQW
SHOYLF QRGHV LQFUHDVHV ZLWK WKHWUHSRUWCHZLWQF1S767FH RI ODWHUDO QRC
LQYROYHPHQW IRU WXPURUV DRHFRWLRQ EHORZ SHULWRQHDO
FRPSDUHG ZLWK IRU WKR VH DRHFRWLRQVFRVH RQ HR\$HULWRQHDO 3HOYLF /F
> @ \$PRQJ WKH WXPURV VLWHDWVWKRCORZ WKH SHULWRQHDO
LQFLGHQFH RI ODWHUDO SHOYLF QRGHV' HVHFWLRQRI QDWVWDOZSWYLF OAPSK
DQDO YHUJH LV DV KLUQFDG HQFH @ ODWHUDOWRQVODW SUHVHQW LV WDLORU
LQYROYHPHQW LV GLUHFWO\ SURSRUWLRQDOWRSDWKRORRDBDQJ7PRVDOHWQFVG
RI ODWHUDO QRGHV LQ S7 S7 DQG \$WELVQXQG &7 SHOYLFQSRVLWURQ HPL
UHVSHFWLYHO\ > @ /DWHUDO SHORRQWKHVHULWLOHRRRQDQDOWHVLCKLJK
WXPURV RU LQ KLJK JUDGH GVSODVLD DVWKRKQKDFYXWVSHQVHRWUFWKQJQDPH
LQ ODWHUDO SHOYLF QRGHV KDV RFFDVLRQDOWRHHQRUHSRQWDFFXUDF\ LQ1SW
WXPURV > @
VSHFLDQ\ RYHUDOO DFFXUDF\ > @ ,Q
PDUJQV DQG LQWHUDQ QRGDO FKDUDFW
LQGLFDWRUV RI PDOLJQDQF\ > @

3URJQRVWLF 9DOXH RI /DWHUDO SHOYLF QRGHV KDV D SRRU SURJQRVWLF IDFWRU ZLWK
\HDU VXUYLYDO UDWH DPRQJ WKR VH ZLWFLVRIROXIDGPRWKLQDSDORQ /DWH
EHLQJ LQ FRQWUDVW WR LQ WKR VH ZLWK XQLQYROYHG QRGHV > @
+RZHYHU D -DSDQHVH 1DWLRQZLGH 0XOWLVWVSHFXWDRQDQWVWVSHRSHUFWLY
PHWDVWDLV LQ ORZ UHFWDO FDQFHU QZLWRQO\ RGDWKHQVLPDQV WKRZQVWVW
HOYLF SURDQVHLQDQWVWVSHUHQFH RI ODWHUDOSH OYLFQRGHVXJWVLEODUWRXUD EQ
PHVRUHFWDQHQDGHVWVW WKDQ GLVWDQW PHWDVWDLV > @ ,Q
DGGLWLRQ SDWLHQWV ZKR KDYH LQYROYHG ODWHUDO SHOYLF QRGHV LQ WK
DEVHQFH RI PHVRUHFWDO QRGHV GR EHWWHU WKDQ WKR VH ZKR KDYH PHVRUHF
QRGHV DOVR LQYROYHG

/RFDO UHFVUHQFH UDWHV RI RU JUHDWU ZDV VHHQ LQ SUH 70(HUD
> @ ZKLFK UHGXFHGVWR EIRVW WKH VWDQGDUG
VXUJLFDQ DSSURDFK IRU UHFWDO FDQFHU /RFDO UHFVUHQFHV ZHUH KLJKHU L
PHQ DQG LQ SDWLHQWV ZLWK ORZ UHFWDO FDQFHU > @ ZKLFK ZDV IXUWKHU
UHGXFHG E\ DGGLWLRQ RI 1\$&757 RU UDGLRWKHUDES\ DORQH 2QH RI WKH
DUJXPHQWV LQ IDYRXU RI /3/1' LV LWV UROH LQ UHGXFHQJ ODWHUDO
UHFVUHQFH \$.RUHQDQ VWXG\ GHPRQVWUDWHG WKDW ODWHUDO SHOYLF OAPSK
QRGHV DUH WKH PDMRU FDXVH RI ORFDO UHFVUHQFH DQG SRRU RYHUDOO VXUYI
LQ ORZ UHFWDO FDQFHU > @ 2Q WKH FRWUDU\ D 6ZHGLVK VWXG\ GLG VKRZ
WKDW ODWHUDO SHOYLF OAPSK QRGH PHWDVWVHV DUH QRW D PDMRU FDXVH RI
UHFVUHQFH DORQH ZLWK PDMRULW\ RI UHFVUHQFH VHHQ DW WKH
DQDVWRPRWLF VLWH > @ \$ UHYLHZ E\ 1LHOVHQ HW DO IRXQG WKDW
DOWKRXXK WKH LQWURGXFWLRQ RI 70(PDGH DQ LPSURYHPHQW LQ FRPSOHWH
UHVHFWLRQ UHFVUHQFHV DW WKH SHOYLF VLGH ZDOO DUH VWLOO FRPPRQ SUR
UHODWHG WR WKH ODWHUDO SHOYLF OAPSK QRGHV > @ 6LPLODUO\ D ODUJH V
IURP -DSDQ IRXQG WKDW DOWKRXXK WKH UDWH RI ORFDO UHFVUHQFH ZDV
VLPLODU EHWZHHQ WKH JURXS ZLWK RU ZLWKRXW /3/1' ODWHUDO SHOYLF
OAPSK QRGH LQYROYHPHQW ZDV DQ LQGHSHQQHQW SUHGLFWRU RI ORFDO
UHFVUHQFH > @ .XVWHUV HW DO LQ WKHLU UHWURVSHFWLYH VWXG\ RI
SDWLHQWV IRXQDQVWVSHUHQ3/1' ODWHUDO UHFVUHQFH
GHYHORSHG LQ RI SDWLHQWV ZKR VKRZHGHQODUJHG ODWHUDO SHOYLF
QRGHV 2Q WKH FRWUDU\ LQ WKR VH SDWLHQWV ZLWKRXW HQODUJHG ODWHU
SHOYLF QRGHV ZKR GLG QRW XQGHUJ /3/1' RQO\ GHYHORSHG ODWHUDO
UHFVUHQFH ODWHUDO VLWH UHFVUHQFH PD\ EH UHGXFHG EXW FDQQRW EH
HOLPLQDWHG LQZD3/1D VLQJOH LQVWLWXWLRQ UHWURVSHFWLYH VWXG\
DQG SDWLHQWV GLG QRW UHFHLYH SUHRSHUDWLYH UDGLDWLRQ WKHUES\ > @
\$NLRVKL HW DO LQ D SURVSHFWLYH VHULHV RI SDWLHQWV RI ZKLFK
SDWLHQWV VKRZHGHQ ODWHUDO SHOYLF QRGHV VHHQ RQ PXOWLSOH GHWHFWR
FRPSXWHG WRPRJUDSK\ &7 RU PDJQHWF UHVRQDQFH LPDJLQJ 05,
DQG SHUVLVWHG SRVW 1\$&757 IRXQG WKDW ORFDO UHFVUHQFH ZDV LQ
WKH 70(RQO\ JURXS DQG LQ /3/1' JURXS WKXV VXSSRUWLQJ
/3/1' LQ SDWLHQWV ZKR VKRZ HQODUJHG ODWHUDO SHOYLF QRGHV SRVW
1\$&757 > @ +RZHYHU WKH\ DOVR IRXQG WKDW UHODWLYHO\ ORZHU

/RQJHU RSHUDWLQJ WLPH JUHDWHU ~~BOFRPSKODDFWKLQFFWLRQDO~~ LPSDLUPHQW
DQGLJQL]FRQWRSHUDWLYH PRUELGLW\ DUH WKH PDLQ FRQVWUDLQV LQ WKH
URXWLQH DSSOLDFWLRQ RI /3/1' > @ 'DPDJH WR WKH K\SRJDVWULF QHUYHV
DQG SHOYLF QHUYH SOH[XV LV WKH PDLQ SDWKRORJ\ UHVSQRVLEOH IRU XULQDU
G\VIXQFWLRQ ZKLFK RFFXUV LQ WR RI SDWLHQWV XQGHUJRLQJ
/3/1' > @ FRQFHSW RI /3/1' ZLWK DXWRQRPRXV QHUYH
SUHVHUYDWLRQ VHPV DWWUDFWLYH LQ WHUPV RI ORZHU LQFLGHQFH RI XULQD
DQG VH[XDO G\VIXQFWLRQ > @ /DSDURVFRSLF DQG URERWLF /3/1' ZLWK
WKH DLG RPDJQL]DWWULFQ\ WR EH DVVRFLDWHG ZLWK
HQFRXUDJLQJ VKRUW WHUP UHVXOWV LQ WKH VKRUW VHULHV UHSRUWHG DOWKR
ORQJ WHUP UHVXOWV DUH VWLOO DZDLWHG > @

Therapeutic /3/1'

*HRUJLRX HW DO > @ GLG D PHWD DQDO\VLV FRPSDULQJ H[WHQGHHG O\PSK
QRGH GLVVHFWLRQ YHUVXV FRQYHQWLRQDO UHFWDQ FDQFHU VXUJHU\ LQ ZKLFK
WKH\ LQFOXGHG SDWLHQWV IURP RQH UDQGRPL]HG WKUHH SURVSHFWLYH
QRQUDQGRPL]HG DQG UHWURVSHFWLYH FDVH FRQWURO VWXGLHV
WKDW WKH\HJJZD]FRQZLWK H[WHQGHHG O\PSK QRGH
GLVVHFWLRQ LQ WHUPV RI VXUYLYDO RU UHFVXUHQFH DOWKRXJK LQWUDRSHUDW
EORRG ORVV GXUDWLRQ RI KRVLWDO VWD\ DQG VH[XDO DQG XULQDU\
G\VIXQFWLRQZ]FDQWZLWK H[WHQGHHG O\PSK QRGH
GLVVHFWLRQ +HQFH WKH\ FRQFOXGHG WKDW H[WHQGHHG O\PSKDGHQHFWRP\
GRHV QRWVLEORJLFDQ DGYDQWJDJH EXW LQFUHDVHG
FRPSOLDFWLRQ +RZHYHU WKLV ZDV EDVHG RQ UHWURVSHFWLYH VWXGLHV
SHUIRUPHG RYHU D ORQJSDUJHQWURWRWHZLWK
EHWZHHQ WKH JURXS

.RED\DVKL HW DO > @ VWXGLHG SDWLHQWV RI ORZ UHFWDQ FDQFHU LQ
ZKLFK /3/1' ZDV GRQH LQ RQFSDWLHQWV RXWFRPHV
ZHUH FRPSDUHG EHWZHHQ WKRVH ZKR KDG XQGHUJRQH /3/1' ZLWK WKRVH
ZKR KDG QRW XQGHUJRQH /3/1' DQG IRXQG WKDW WKH WZR JURXS ZHUH
FRPSDUDEOH LQ WHUPV RI UHFVXUHQFH DQG
VXUYLYDO +RZHYHU LW ZDV IRXQG WKDW LQYROYHPHQW RI ODWHUDO SHOYLF QR
ZDV DQ LQGHSHQGHQW SRRU SURJQRVWLF IDFWRU DQG LQGLFDWRU RI ORFDO
UHFVXUHQFH

:DWDQDEH HW DO > @ UHWURVSHFWLYHO\ UHYLHZHG SDWLHQWV RI UHFWDQ
FDQFHU WUHDWHG DW WKHLU FHQWHU :KROH FRKRUW RI SDWLHQWV ZDV GLYLG
LQWR IRXU JURXS EDVHG RQ WKH\RXQR 1\$&57 DQG /3/1'
WKDW WKH\HJJZD]FDQW VXUYLYDO DGYDQWJDJH ZLWK WKH XVH RI
SUHRSHUDWLYH &57 +RZHYHUFDQWZDV QR
RYHUGOO VXUYLYDO RU ORFDO UHFVXUHQFH EHWZHHQ WKH SDWLHQWV ZKR KD
QHRDGMXYDQW UDGLRWKHU\S ZLWK FRQYHQWLRQDO VXUJHU\ FRPSDUHG ZLWK
WKRVH ZKR KDG FRQYHQWLRQDO VXUJHU\ ZLWK /3/1' ZLWKRXW 1\$&57
6LPLODU UHVXOWV ZHUH DOVR VHHQ ZKHQ WKH UHVXOWV RI UHFWDQ FDQFHU
WUHDWPHQW IROORZHG LQ WKH 1HWKHUODQGV DQG -DSDQ ZHUH FRPSDUHG

\$NL\RVKL HW DO > @ VWXGLHG WKH UROH RI /3/1' LQ SDWLHQWV RI
ORFDOO\ DGYDQFHG ORZ UHFWDQ FDUFLQRPD ,Q WKLV VWXG\ /3/1' ZDV
RvHUVHSHFWLYHO\ WR WKRVH SDWLHQWV ZKR KDG HQODUJHG ODWHUDO SHOYLF
QRGHV RQ LPDJLQJ EHIRUH 1\$&757)RU WKRVH LQ ZKRP ODWHUDO SHOYLF
QRGHV ZHUH QRW HQODUJHG R-108 70(ZDV SHUIRUPHG
H\ IRXQG WKDW WKUHH SDWLHQWV LQ WKH 70(JURXS GHYHORSHG ORFDO
UHFVXUHQFH LQ ODWHUDO SHOYLF QRGHV LQ FRQWUDV WR QRQH LQ /3/1' JURXS
ZKLFK ZDV VWDLQLVFDQWZLWK DQDO\VLV
SDWKRORJLFDQ QRGDO VWDJH ZDV WKH RQO\ LQGHSHQGHQW SURJQRVWLF IDFWRU
SUHGLFWLQJ UHODSVH IUHH VXUYLYDO 6R WKH DXWKRUV DGYRFDWHG WKH
DSSOLDFWLRQ RI /3/1' LQ WKRVH SDWLHQWV RI ORZ UHFWDQ FDQFHU ZKR
VZRZHG HQODUJHG ODWHUDO SHOYLF QRGHV RQ LPDJLQJ EHIRUH 1\$&757 ,Q
WKLV VWXG\ WKH\ REVHUYHG WKDW LQ DOO RI WKH SDWLHQWV ZLWK HQODUJHG
RQ SUH 1\$&757 05, UHYHDOHG 8757LGXDO QRGHV

<DQR + 0RUDQH%LQFLGHQFH RI ODWHUDO SHOYLF VLGH ZDOO QRGDO
LQYROYHPPHQW LQ ORZ UHFWDQ FDQFHU PD\ EH VLPLODU LQ -DSDQ DQG WKH :HVW %U
- 6XUJ

8HQR 0 2\D 0 \$JHNXUD . <DPDJXFKL 7 0XWR 7 ,QFLGHQFH DQG
SURJQV\JQLF FDQFHUWHUDO O\PSK QRGH PHWDVWDVLV LQ SDWLHQWV ZLWK
DGYDQFHG ORZ UHFWDQ FDQFHU %U - 6XUJ

8HQR + 0RFKLJXNL + +DVKLJXFKL < ,VKLJXUR 0 0L\RVKL 0 HW DO
3RWHQWLDEHSHR\QDWHUWHU SHOYLF QRGH GLVVHFWLRQ IRU
UHFWDQ FDQFHU ORFDWHG-ER\QDWHU SHULWRQHDO

0(5&85< 6WXG\ *URXS 6KLDDE 2& 7D\ORU) %HHV 1 %ODNH + HW DO
5HOHYDQFH RI PDJQHWF UHVRQDQFH LPDJLQJ GHWHFWHG SHOYLF VLGHZDOO
O\PSK QRGH LQYROYHPPHQW LQ UHFWDQ FDQFHU %U - 6XUJ

6XHGD 1RXUD 6 2KXH 0 6KLQDL 7 ,PDGD 6 HW DO &DVH RI
LVRODWHG ODWHUDO O\PSK QRGH UHFWDQ FDQFHU RFFXUULQJ
UHFWDQ FDQFHU WUHDWHG ZLWK ODWHUDO O\PSK QRGH GLVVHFWLRQ UHSRUW RI D FDV