Optimal Vascular Access Choice for Patients on Hemodialysis

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Online Supplement

Part A of the online supplement provides some general results that are used in Part B, which contains the proof of the analytical results of the paper.

Part A: General Results

Lemma 1. *Each of the following are equivalent to* $X \leq_{hr} Y$*:*

1. $X_t \leq_{st} Y_t, \forall t$
2. $\dfrac{\overline{\mathbf{F}}_{\mathbf{X}}(t)}{\overline{\mathbf{F}}_{\mathbf{Y}}(t)}$ *is decreasing in* t.

Proof. For (1) see Equation 1.B.7 in Shaked and Shanthikumar (2007). For (2), see Theorem 1.3.3 in Müller and Stoyan (2002). ■

Lemma 2 (Closure of stochastic order under mixture)**.** *Let* X*,* Y *be two random variables such that for all realizations of the random vector* $\boldsymbol{Z}$*, we have* $[X|\boldsymbol{Z}=\boldsymbol{z}] \leq_{st} [Y|\boldsymbol{Z}=\boldsymbol{z}]$*. Then,* $X \leq_{st} Y$*.*

Proof. The proof directly follows Theorem 1.2.15 in Müller and Stoyan (2002). ■

Lemma 3. *Assumption 4 is equivalent to having that* $\dfrac{\overline{\mathbf{F}}_{\mathbf{C}}(t)}{\overline{\mathbf{F}}_{\mathbf{A}}(t)}$ *is a log-convex function of* t.

Proof. Note that $\frac{d}{dt}\ln \overline{\mathbf{F}}_{\mathbf{X}}(t) = -\mathbf{r}_{\mathbf{X}}(t)$. Since $\frac{d}{dt}\ln \dfrac{\overline{\mathbf{F}}_{\mathbf{C}}(t)}{\overline{\mathbf{F}}_{\mathbf{A}}(t)} = \frac{d}{dt}\ln \overline{\mathbf{F}}_{\mathbf{C}}(t) - \frac{d}{dt}\ln \overline{\mathbf{F}}_{\mathbf{C}}(t) = \mathbf{r}_{\mathbf{A}}(t) - \mathbf{r}_{\mathbf{C}}(t)$, the result follows from Assumption 4 and the fact that a differentiable function is convex if and only if its derivative is increasing. ■

Lemma 4. *Assume that* g *is a differentiable and log-convex function. Then,* $\frac{g(x)}{g(x+a)}$ *is decreasing in* x *for any* $a \geq 0$.

Proof. It suffices to show that $\ln \frac{g(x)}{g(x+a)} = \ln g(x) - \ln g(x+a)$ is decreasing in x. Define $G := \ln g$, a convex function by assumption. Since $\frac{d}{dx}\ln \frac{g(x)}{g(x+a)} = \frac{d}{dx}G(x) - \frac{d}{dx}G(x+a) \leq 0$, based on the fact that the derivative of a convex function is increasing, we have that $\ln \frac{g(x)}{g(x+a)}$ is decreasing in x. ■

Lemma 5. *If the random variable* X *is IFR, then* X_t *is stochastically decreasing in* t.

Proof. Choose $t \leq t'$ and $s \geq 0$, arbitrarily. We have $\mathbf{r}_{\mathbf{X}_{\mathbf{t}'}}(s) = \mathbf{r}_{\mathbf{X}}(t'+s)$ and $\mathbf{r}_{\mathbf{X}_{\mathbf{t}}}(s) = \mathbf{r}_{\mathbf{X}}(t+s)$. Since X has the IFR property, we have $\forall s, \mathbf{r}_{\mathbf{X}_{\mathbf{t}}}(s) \leq \mathbf{r}_{\mathbf{X}_{\mathbf{t}'}}(s)$. Thus, $X_{t'} \leq_{hr} X_t$ by definition which implies $X_{t'} \leq_{st} X_t$, because hazard rate order implies the stochastic order (see Lemma 1). ■

Lemma 6. *If $\overline{\mathbf{F}}_{\mathbf{X}}(t)$ is differentiable, then the mean residual lifetime of a random variable X is differentiable. Moreover, we have:* $\frac{d}{dt}\mathbb{E}X_t = \mathbf{r}_{\mathbf{X}}(t)\mathbb{E}X_t - 1$.

Proof. See Gupta and Bradley (2003). ■

Part B: Proofs for Analytical Results

We provide proofs in three sections. Proof of Theorem 1 is given in the first section. The second section includes proofs for Theorems 2-5, Corollaries 1-2, and Proposition 1. The final section provides proofs for Theorems 6 and 7.

Proof of Theorem 1:

We first prove a preliminary lemma that facilitates proving the main results.

Lemma 7. *Assumptions 3-5 apply to A_t and C_t as well. In other words, for all $s, t \geq 0$, we have $C_t \leq_{hr} A_t$, $\mathbf{r}_{\mathbf{C}_{\mathbf{t}}}(s) - \mathbf{r}_{\mathbf{A}_{\mathbf{t}}}(s)$ is decreasing in s, and $\mathbf{r}_{\mathbf{A}_{\mathbf{t}}}(s)$, $\mathbf{r}_{\mathbf{C}_{\mathbf{t}}}(s)$ are increasing in s.*

Proof. The result follows by noting that $\mathbf{r}_{\mathbf{X}_{\mathbf{t}}}(s) = \mathbf{r}_{\mathbf{X}}(t+s)$ for any random variable X, and $t, s \geq 0$. ■

In what follows, we let K_i denote the lifetime of the i^{th} AVF, i.e., $K_i = 0$, if the i^{th} AVF does not mature and $K_i = Z_i$, if otherwise.

Proof of Theorem 1. We prove Theorem 1 for all realization of M_i, and K_i for $i = 1, \ldots, N$, where N is the total number of AVF chances. Since AVF creation variables are not affected by the policy in use based on Assumption 6, the result generalizes using Lemma 2 (closure of stochastic order under mixture).

Let $L(t, n)$ denote a patient's residual lifetime at t, given n remaining AVF chances, under the optimal policy (one that maximizes a patient's survival function probability for each time t). Suppose one could set the AVF use time (rather than setting the surgery time) at $t + u$. Let $L(u)$ be a patient's residual lifetime at time t when we plan to use current AVF at $t + u$ and follow the optimal policy for the subsequent $n - 1$ AVF chances. We prove that $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is decreasing in u (for any a). Since for y, the surgery time, we have $y = u - m_i$, this is equivalent to proving that the residual lifetime stochastically decreases in y.
→ **Base case: n=1:** Based on Assumption 2 on a patient's survival, we can calculate $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ for different values of u, a, k as follows (see Figure 1).

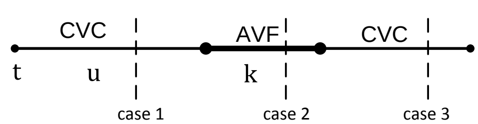

Figure 1: Possible cases for $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$.

- Case 1: $a \leq u$: We have $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a) \overset{(*)}{=\!=} \mathbb{P}[C_t > a] = \overline{\mathbf{F}}_{\mathbf{C}_{\mathbf{t}}}(a)$.
- Case 2: $[a-k]^+ \leq u \leq a$: We have

$$\overline{\mathbf{F}}_{\mathbf{L(u)}}(a) = \mathbb{P}[C_t > u, A_{t+u} > a-u] = \mathbb{P}[C_t > u]\mathbb{P}[A_{t+u} > a-u \big| C_t > u]$$
$$\overset{(*)}{=\!=} \mathbb{P}[C_t > a]\mathbb{P}[A_{t+u} > a-u] \overset{(*)}{=\!=} \mathbb{P}[C_t > u].\mathbb{P}[A_t > a | A_t > u] = \overline{\mathbf{F}}_{\mathbf{C}_{\mathbf{t}}}(u)\frac{\overline{\mathbf{F}}_{\mathbf{A}_{\mathbf{t}}}(a)}{\overline{\mathbf{F}}_{\mathbf{A}_{\mathbf{t}}}(u)}$$

- Case 3: $0 \le u \le [a-k]^+$: We have:

$$\begin{aligned}
\overline{\mathbf{F}}_{\mathbf{L(u)}}(a) &= \mathbb{P}[C_t > u, A_{t+u} > a-u, C_{t+u+k} > a-(u+k)] \\
&= \mathbb{P}[C_t > u].\mathbb{P}[A_{u+t} > k \big| C_t > u].\mathbb{P}[C_{u+k} > a-(u+k) \big| A_{t+u} > k, C_t > u] \\
&\overset{(*)}{=\!=} \mathbb{P}[C_t > u].\mathbb{P}[A_t > k+u \big| A_t > u].\mathbb{P}[C_t > a \big| C_t > u+k] \\
&\overset{(*)}{=\!=} \overline{\mathbf{F}}_{\mathbf{C_t}}(u).\frac{\overline{\mathbf{F}}_{\mathbf{A_t}}(k+u)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)}\frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(a)}{\overline{\mathbf{F}}_{\mathbf{C_t}}(u+k)} = \overline{\mathbf{F}}_{\mathbf{C_t}}(a).\frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(u)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)} / \frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(u+k)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u+k)}
\end{aligned}$$

in which $(*)$ represents implication by Assumption 2. Note that $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is continuous within each range, and its value on the boundary points coincides. Therefore, it suffices to prove that in each range, $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is decreasing. In Case 1, the function is constant and thus the result holds trivially. In Case 2, since $C_t \le_{hr} A_t$ according to Lemma 7 (which requires Assumptions 3-5), the function is decreasing using Lemma 1. In Case 3, Lemma 7 and Lemma 3 imply that $\frac{\overline{\mathbf{F}}_{\mathbf{C_t}}(u)}{\overline{\mathbf{F}}_{\mathbf{A_t}}(u)}$ is log-convex in u. Using Lemma 4, we have that $\overline{\mathbf{F}}_{\mathbf{L(u)}}(a)$ is decreasing in u.

Let $L(t,n,u)$ be the patient's residual lifetime at t when we use the current AVF chance at $t+u$ and follow the optimal policy for the subsequent AVF chances. We now present the induction step:
$\rightarrow$ **Induction step:** Assume $L(t,n-1,u_2) \le_{st} L(t,n-1,u_1)$, for all $u_1 \le u_2$. We prove that if $u_1 \le u_2$, then $L(t,n,u_2) \le_{st} L(t,n,u_1)$.

To calculate the lifetime of the patient for the case of multiple AVF chances, we assume that AVFs are created sequentially and never in parallel (supported by Assumption 1). Since stochastic order is a partial order, using the transitivity property we can instead prove that $L(u_2) \le_{st} L'$ and $L' \le_{st} L(u_1)$, in which L' is the lifetime under a hypothetical situation similar to $L(u_1)$ with the difference that the decision to use the subsequent AVF is delayed until u_2+k (see Figure 2).

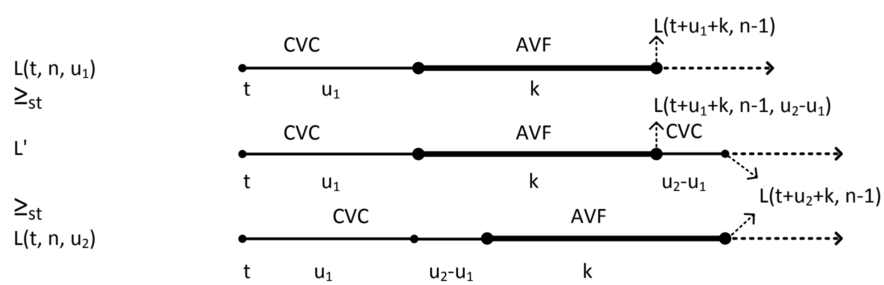

Figure 2: Induction step and the hypothetical random variable L'.

- $L(u_2) \le_{st} L'$: For $x \le u_2+k$, we have that $\overline{\mathbf{F}}_{\mathbf{L(u_2)}}(x) = \overline{\mathbf{F}}_{\mathbf{L(t,1,u_2)}}(x)$ and $\overline{\mathbf{F}}_{\mathbf{L'}}(x) = \overline{\mathbf{F}}_{\mathbf{L(t,1,u_1)}}(x)$. Thus the result follows from induction base. Otherwise, we have

$$\begin{aligned}
\overline{\mathbf{F}}_{\mathbf{L(u_2)}}(x) &= \overline{\mathbf{F}}_{\mathbf{L(u_2)}}(u_2+k).\overline{\mathbf{F}}_{\mathbf{L(u_2+k,n-1)}}(x-[u_2+k]), \\
\overline{\mathbf{F}}_{\mathbf{L'}}(x) &= \overline{\mathbf{F}}_{\mathbf{L'}}(u_2+k).\overline{\mathbf{F}}_{\mathbf{L(u_2+k,n-1)}}(x-[u_2+k]).
\end{aligned}$$

  Based on the previous result, we have $\overline{\mathbf{F}}_{\mathbf{L(u_2)}}(u_2+k) \le \overline{\mathbf{F}}_{\mathbf{L'}}(u_2+k)$, and thus we get the result.

- $L' \le_{st} L(t,n,u_1)$. For $x \le u_1+k$, we have that $\overline{\mathbf{F}}_{\mathbf{L(u_1)}}(x) = \overline{\mathbf{F}}_{\mathbf{L'}}(x) = \overline{\mathbf{F}}_{\mathbf{L(t,1,u_1)}}(x)$. For $x \ge u_1+k$,

$$\begin{aligned}
\overline{\mathbf{F}}_{\mathbf{L(u_1)}}(x) &= \overline{\mathbf{F}}_{\mathbf{L'}}(u_1+k).\overline{\mathbf{F}}_{\mathbf{L(u_1+k,n-1,0)}}(x-[u_1+k]), \\
\overline{\mathbf{F}}_{\mathbf{L'}}(x) &= \overline{\mathbf{F}}_{\mathbf{L'}}(u_1+k).\overline{\mathbf{F}}_{\mathbf{L(u_1+k,n-1,u_2-u_1)}}(x-[u_1+k]).
\end{aligned}$$

  Using the induction hypothesis, we have $L(u_1+k,n-1,u_2-u_1) \le_{st} L(u_1+k,n-1,0)$, and thus we have the desired result.

■

Proofs of Theorems 2, 3-5, Corollaries 1-2, and Proposition 1:

We prove the optimality of threshold policies (Theorem 3) in three steps. First in Proposition 2, we prove the existence of an optimal HD-duration threshold policy for the case $n = 1$. Next, we prove Theorems 4-5 and Corollary 1 for the special case $n = 1$. Finally, using these results, we prove that the same threshold policy formed in Proposition 2 is optimal for the case $n > 1$, as well.

We use the following notations in what follows.

- $v^{\pi}(NF, n, t)$: the value function (the remaining QALE of a patient) at state (NF, n, t) under an arbitrary policy π
- $v(NF, n, t, y)$: the value function of the policy consisting of surgery planned at $t + y$ for the current AVF chance and then the optimal policy for the subsequent decisions.
- $v(NF, n, t)$: the optimal value function at state (NF, n, t).

Note that we supposed Assumptions 1-2 and 6 in defining the dynamic programming model (see Section 3.4). Let π_0 denote the policy of using CVC for the rest of the patient's life (hereafter referred to as the "no-AVF" policy). Under this policy, the patient remains on a CVC until she dies, and since her residual lifetime under this policy is C_t, her QALE is $q_c\mathbb{E}[C_t]$, i.e., we have $\forall NF, n : v^{\pi_0}(NF, n, t) = q_c\mathbb{E}C_t$. Since $v^{\pi_0}(NF, n, t) = q_c\mathbb{E}C_t$ for any NF and n, we use $v^{\pi_0}(., ., t)$ to denote this independence.

Let s denote a general patient state. Note that the value function of an arbitrary policy π, i.e., $v^{\pi}(s)$, is the expected quality adjusted lifetime of a patient under that policy. In what follows, we let $v^{\pi}(s|\mathcal{E})$ represent the value function of the policy π conditional on an event $\mathcal{E}$. For instance, $\big(v^{\pi_1}(s) - v^{\pi_2}(s)\big|C_t \leq y\big)$ denotes the QALE difference between two arbitrary policies π_1 and π_2 conditional on the event $C_t \leq y$.

We use Lemmas 8-10 to prove Proposition 2.

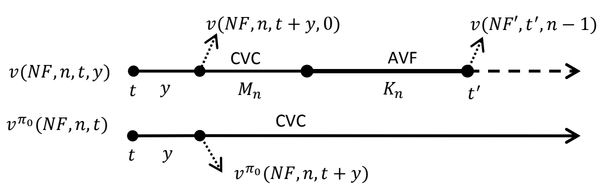

Figure 3: Linking $v(NF, n, t, y)$, $v(NF, n, t + y, 0)$, and $v^{\pi_0}(NF, n, t + y)$.

Lemma 8. *The following equality holds for $v(NF, n, t, y)$.*

$$v(NF, n, t, y) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\Big[v(NF, n, t + y, 0) - v^{\pi_0}(., ., t + y)\Big] + v^{\pi_0}(., ., t)$$

Proof. Consider Figure 3. We want to prove that the difference between the value functions of the policy consisting of surgery planned at $t + y$ for the current AVF chance and then the optimal policy for the subsequent decisions and the no-AVF policy, i.e., $v(NF, n, t, y) - v^{\pi_0}(., ., t)$, equals $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)\big[v(NF, n, t + y, 0) - v^{\pi_0}(., ., t + y)\big]$.

If $C_t \leq y$, then the patient dies before the AVF surgery, in which case there is no difference between the two policies. If $C_t > y$, which happens with probability $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)$, then the difference between the two policies equals the difference between the value function at the state $(NF, n, t+y)$ when we follow the policy consisting of immediate surgery for the current AVF chance and then the optimal policy for the subsequent decisions and that of the same state but following the no-AVF policy, i.e., $v(NF, n, t + y, 0) - v^{\pi_0}(., ., t + y)$. Therefore, we have $v(NF, n, t, y) - v^{\pi_0}(., ., t) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\big[v(NF, n, t + y, 0) - v^{\pi_0}(., ., t + y)\big]$ and thus the result. ■

For Lemma 9, let $w(t, m, k)$ denote the residual HD utility adjusted lifetime expectancy of a patient at time t (which is the patient's QALE without subtracting the AVF creation disutility) under a scenario in which the patient undergoes the surgery at t for her only AVF chance and the AVF maturation time and AVF lifetime are deterministically set at m and k, respectively.

Based on Assumption 2 on a patient's survival, we can calculate $w(t,m,k)$ as follows:

$$w(t,m,k) = q_c \int_0^m x\mathbf{f}_{\mathbf{C_t}}(x)dx + \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[q_c m + q_a \int_0^k x\mathbf{f}_{\mathbf{A_{t+m}}}(x)dx + \overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\big[q_a k + q_c \mathbb{E}C_{t+m+k}\big]\Big]. \tag{1}$$

We can express $v(NF,1,t,0)$ and $v^{\pi_0}(.,.,t)$ using $w(t,m,k)$ as follows:

$$v(NF,1,t,0) = -d + \mathbb{E}_{M,K|NF}[w(t,m,k)], \tag{2}$$
$$v^{\pi_0}(.,.,t) = w(t,m,0) : \forall m. \tag{3}$$

We will use these equalities in later proofs.

Lemma 9. *Suppose Assumptions 2-5 and 8. We have $\frac{\partial}{\partial k}w(t,m,k)$ is non-negative and decreasing in t and m.*

Proof. To have differentiability of w in k, it suffices to assume that $\overline{\mathbf{F}}_{\mathbf{A}}(x)$ and $\overline{\mathbf{F}}_{\mathbf{C}}(x)$ are differentiable at all values of x because they in turn imply that $\overline{\mathbf{F}}_{\mathbf{A_t}}(x)$ and $\overline{\mathbf{F}}_{\mathbf{C_t}}(x)$ (as a direct result) and $\mathbb{E}C_x$ (using Lemma 6) are differentiable functions in x.

We have:

$$\frac{\partial}{\partial k}w(t,m,k) = \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[\frac{d}{dk}q_a \int_0^k x\mathbf{f}_{\mathbf{A_{t+m}}}(x)dx + \overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\frac{d}{dk}\big[q_a k + q_c \mathbb{E}C_{t+m+k}\big] + \big[\frac{d}{dk}\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\big]\big[q_a k + q_c \mathbb{E}C_{t+m+k}\big]\Big] \tag{4}$$

$$= \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[q_a k\mathbf{f}_{\mathbf{A_{t+m}}}(k) + \overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\big\{q_a + q_c\big[\mathbf{r}_{\mathbf{C_{t+m}}}(k)\mathbb{E}C_{t+m+k} - 1\big]\big\} - \mathbf{f}_{\mathbf{A_{t+m}}}(k)[q_a k + q_c \mathbb{E}C_{t+m+k}]\Big] \tag{5}$$

$$= \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)\Big[q_a - q_c + q_c \mathbb{E}C_{t+m+k}\big[\mathbf{r}_{\mathbf{C_t}}(m+k) - \mathbf{r}_{\mathbf{A_t}}(m+k)\big]\Big] \tag{6}$$

where Equation 4 follows from Equation 1 using the product rule in calculating the derivatives of products of two functions, Equation 5 follows from Equation 4 by using Lemma 6, and finally Equation 6 follows from Equation 5 by rearranging terms.

We can prove that $\frac{\partial}{\partial k}w(t,m,k)$ is decreasing in t and non-negative by showing that it is a product of the following three non-negative decreasing functions:

1. $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$: This is decreasing in t, since C_t is stochastically decreasing in t based on Lemma 5 and that C is IFR by Assumption 5.
2. $\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)$: This is decreasing in t, since A_{t+m} is stochastically decreasing in t based on Lemma 5 and that A is IFR by Assumption 5.
3. $q_a - q_c + q_c \mathbb{E}C_{t+m+k}\big[\mathbf{r}_{\mathbf{C_t}}(m+k) - \mathbf{r}_{\mathbf{A_t}}(m+k)\big]$:
    - non-negative: We have that $q_a \geq q_c$ by Assumption 8. Also, $\mathbf{r}_{\mathbf{C_t}}(m+k) \geq \mathbf{r}_{\mathbf{A_t}}(m+k)$ based on Lemma 7 (which requires Assumptions 3-5).
    - decreasing: $\mathbb{E}C_{t+m+k}$ is decreasing in t, because C_{t+m+k} is stochastically decreasing in t by Lemma 5 and the fact that C is IFR by Assumption 5. Also, $\mathbf{r}_{\mathbf{C_t}}(m+k) - \mathbf{r}_{\mathbf{A_t}}(m+k)$ is decreasing in t based on Lemma 7.

Using the same logic, we can show that $\frac{\partial}{\partial k}w(t,m,k)$ is decreasing in m.

■

Lemma 10. *Suppose Assumptions 2-6 and 8. For any NF, we have $v(NF,1,t,0) - v^{\pi_0}(.,.,t)$ is decreasing in t.*

Proof. Choose $t_1 \leq t_2$, arbitrarily. We have that $\forall m : \frac{\partial}{\partial k}[w(t_2,m,k) - w(t_1,m,k)] \leq 0$ by the linearity of the differential operator and Lemma 9 (which requires Assumptions 2-5 and 8). This implies that

$$\forall k,m : w(t_2,m,k) - w(t_1,m,k) \leq w(t_2,m,0) - w(t_1,m,0).$$

But by Equation 3 we have: $\forall m,t : w(t,m,0) = v^{\pi_0}(.,.,t)$. Thus,

$$\forall k,m : w(t_2,m,k) - w(t_1,m,k) \leq v^{\pi_0}(.,.,t_2) - v^{\pi_0}(.,.,t_1).$$

Taking expectation from both sides with respect to $M,K|NF$ and Equation 2 gives us:

$$v(NF,1,t_2,0) - v(NF,1,t_1,0) \leq v^{\pi_0}(.,.,t_2) - v^{\pi_0}(.,.,t_1).$$

Note that taking expectation is justified based on Assumption 6. By rearranging the terms in the above inequality, we obtain the desired result. ■

Proof of Theorem 2. This result is in fact a corollary to Lemma 10. By assuming $d = 0$, $M = 0$, and $K = \infty$ with probability 1, we obtain $v(NF,1,t,0) = q_A \mathbb{E} A_t$. Since $v^{\pi_0}(.,.,t) = q_C \mathbb{E} C_t$ by definition, we have that $q_A \mathbb{E}[A_t] - q_C \mathbb{E}[C_t]$ is decreasing in t. The result then follows by assuming $q_A = q_C = 1$. ■

Proposition 2 (Existence of Threshold Policies for $n = 1$)**.** *Assume $n = 1$ and fix NF, arbitrarily. Under Assumptions 2-6 and 8, there exists a threshold policy $\tau^*(NF)$ that maximizes the QALE of the patient.*

Proof. Fix t, and NF, arbitrarily. Assume that we plan the surgery at $t + y$. By Lemma 8, we have:

$$v(NF,1,t,y) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\Big[v(NF,1,t+y,0) - v^{\pi_0}(.,.,t+y)\Big] + v^{\pi_0}(.,.,t)$$

For this decision to be an optimal action, it is necessary that surgery at $t + y$ is no worse than the no-AVF policy, i.e., $v(NF,1,t+y,0) \geq v^{\pi_0}(.,.,t+y)$.
Since $v(NF,1,t+y,0) - v^{\pi_0}(.,.,t+y)$ is decreasing in y by Lemma 10 (which requires Assumptions 2-6 and 8), and $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)$ is decreasing in y, then $v(NF,1,t,y)$ is decreasing in y for all y that satisfy the necessary condition. Thus, the optimal action is to perform surgery at t if $v(NF,1,t,0) \geq v^{\pi_0}(.,.,t)$, and no surgeries, if otherwise.

Now, we form the policy τ^* as follows based on whether $v(NF,1,0,0) \leq v^{\pi_0}(.,.,0)$ or not.

- $v(NF,1,0,0) \leq v^{\pi_0}(.,.,0)$: we have that for $\forall t : v(NF,1,0,0) \leq v^{\pi_0}(.,.,0)$, since $v(NF,1,t,0) - v^{\pi_0}(.,.,t)$ is decreasing in t by Lemma 10. As a result, the no AVF surgery (i.e., "CVC forever") is optimal for all t. Choose $\tau^*(NF) = 0$ in this case.
- $v(NF,1,0,0) > v^{\pi_0}(.,.,0)$: we have that $\exists t' \leq \infty$ such that for $t < t'$, we have $v(NF,1,0,0) > v^{\pi_0}(.,.,0)$, and $v(NF,1,0,0) \leq v^{\pi_0}(.,.,0)$ for $t \geq t'$ because $v(NF,1,t,0) - v^{\pi_0}(.,.,t)$ is decreasing in t. For $t < t'$, surgery at t is optimal, and for $t \geq t'$, the patient should remain on a CVC, i.e., the no surgery policy is optimal. Choose $\tau^*(NF) = t'$ in this case.

The policy $\tau^*(NF)$ is optimal for $n = 1$ by construction. ■

Now that we have achieved the first step in proving the optimality of threshold policies, we prove Theorems 4-5 and Corollary 1 for the special case $n = 1$. Once we prove the optimality of $\tau^*(NF)$ for all n in Theorem 3, which requires Assumptions 1-8, these results also generalize.

Proof of Theorem 4 for $\boldsymbol{n = 1}$. Based on the way we constructed $\tau^*(NF; d)$ in Proposition 2, we have:

$$t \geq \tau^*(NF; d) \iff v(NF,1,t,0; d) \leq v^{\pi_0}(.,.,t). \tag{7}$$

Define $d^{\text{cr}}(NT,t)$ as follows:

$$d^{\text{cr}}(NF,t) := \mathbb{E}_{M,K|NF}[w(t,m,k)] - v^{\pi_0}(.,.,t). \tag{8}$$

Note that by Equation 2, we have:

$$d^{\mathrm{cr}}(NF,t) = d + v(NF,1,t,0) - v^{\pi_0}(.,.,t). \tag{9}$$

By Equation 7 and the above equality, we have:

$$t \geq \tau^*(NF) \iff d^{\mathrm{cr}}(NF,t) \leq d \tag{10}$$

Thus, $d^{\mathrm{cr}}(NF,t)$ is indeed a critical value for AVF creation disutility in determining the optimal decision. ■

Proof of Theorem 5 for $\boldsymbol{n=1}$. We have:

$$\begin{aligned} d^{\mathrm{cr}}(NF,t) &= \mathbb{P}[K=0|NF]\mathbb{E}_M[w(t,m,0)] + \mathbb{P}[K>0|NF]\mathbb{E}_{M,Z}[w(t,m,z)] - v^{\pi_0}(.,.,t) && (11)\\ &= \mathbb{P}[K=0|NF]v^{\pi_0}(.,.,t) + \mathbb{P}[K>0|NF]\mathbb{E}_{M,Z}[w(t,m,z)] - v^{\pi_0}(.,.,t) && (12)\\ &= \mathbb{P}[B=1|NF]\big(\mathbb{E}_{M,Z}[w(t,m,z)] - v^{\pi_0}(.,.,t)\big), && (13)\end{aligned}$$

where Equation 11 follows from the definition of $d^{\mathrm{cr}}(NF,t)$ in Equation 8, the law of total probability and definitions of K and Z, Equation 12 follows from Equation 11 by using the fact $v^{\pi_0}(.,.,t) = w(t,m,0)$ (see Equation 3), and Equation 13 follows from Equation 12 by rearranging terms. ■

Note that we can use Equation 13 to numerically calculate the critical disutility by calculating $\mathbb{E}_{M,Z}[w(t,m,z)]$, either by Monte-Carlo simulation or analytically, and $v^{\pi_0}(.,.,t)$ using the equality $v^{\pi_0}(.,.,t) = q_c\mathbb{E}C_t$.

Proof of Corollary 1 for $\boldsymbol{n=1}$.
By Equation 13, we have $d^{\mathrm{cr}}(NF,t) = \mathbb{P}[B=1|NF]\big(\mathbb{E}_{M,Z}[w(t,m,z)] - v^{\pi_0}(.,.,t)\big)$. By Assumption 7, the AVF surgery success probability is decreasing in NF. Therefore, we have that the critical disutility is decreasing in NF for any t.

Choose $NF_1 \leq NF_2$, arbitrarily. Let $t_i = \tau^*(NF_i)$ for $i=1,2$. By Equation 10, we have $d^{\mathrm{cr}}(NF_1,t_1) \geq d$ (substitute t_1 for t and NF_1 for NF). Since the critical disutility is decreasing in NF for any t, we have $d^{\mathrm{cr}}(NF_2,t_1) \leq d$, as well. By Equation 10, we have $t_2 \leq t_1$ (substitute t_2 for t and NF_2 for NF). ■

Before proving Theorem 3, we show the following property for τ^*.

Proposition 3. *For* τ^**, we have:*

1. $\forall n, NF, t : v^{\tau^*}(NF,n,t) \geq v^{\pi_0}(.,.,t)$,
2. $\forall n, NF : v^{\tau^*}(NF,n,t) - v^{\pi_0}(.,.,t)$ *is decreasing in* t.

Proof. Fix NF, arbitrarily. We prove the result by induction on n as follows:

- $n=1$: We have:

$$v^{\tau^*}(NF,1,t) - v^{\pi_0}(.,.,t) = \begin{cases} v(NF,1,t,0) - v^{\pi_0}(.,.,t) & : t < \tau(NF) \\ 0 & : o.w. \end{cases}$$

  The function is decreasing for $t < \tau(NF)$ by Lemma 10, and for $t \geq \tau(NF)$ trivially. It suffices to have that $v^{\tau^*}(NF,1,t) \geq v^{\pi_0}(.,.,t)$, which follows from the fact that τ^* is optimal for $n=1$.

- Assume the result holds for $n = 1,\ldots,l$. We prove that it holds for $n = l+1$.

  For $t \geq \tau^*(NF)$, we have $v^{\tau^*}(NF,l+1,t) = v^{\pi_0}(.,.,t)$, since the two policies coincide. For $t < \tau^*(NF)$, fix $M=m$, and $K=k$ for the current AVF chance, arbitrarily. The result generalizes by taking expectation. Let $t' = t+m+k$ and $NF' = NF+1$, if $k=0$, and $NF' = NF$, otherwise. We have:

$$v^{\tau^*}(NF,l+1,t) - v^{\tau^*}(NF,1,t) = S(t,t')\big[v^{\tau^*}(NF',l,t') - v^{\pi_0}(.,.,t')\big]. \tag{14}$$

  where $S(t,t')$ represent the probability of survival of the patient until time t'. We can explain Equation 14 as follows. The difference, in terms of QALE, between the states $(NF,l+1,t)$ and $(NF,1,t)$ under the policy τ^* does not start until t', which is realized only if the patient survives until t' with probability $S(t,t')$. At t', the patient receives $v^{\tau^*}(NF',l,t')$ for the case we start by $l+1$ AVF chances, whereas for the case we start by one AVF chance, the patient switches to a CVC forever at t' and receives $v^{\pi_0}(.,.,t')$. Therefore, we have

$$v^{\tau^*}(NF,l+1,t) \geq v^{\tau^*}(NF,1,t) \geq v^{\pi_0}(.,.,t),$$

where the first inequality results from Equation 14 and that $v^{\tau^*}(NF',l,t') \geq v^{\pi_0}(.,.,t')$ by induction assumption, and the second inequality results from induction basis. This proves the first property.

Since $v^{\tau^*}(NF,1,t) - v^{\pi_0}(.,.,t)$ is decreasing in t, in order to prove the second property, it suffices to prove that the right-hand side of Equation 14 is decreasing in t. We prove it by showing that it is the product of the following two non-negative and decreasing functions:

1. $S(t',t)$: The probability is non-negative by definition. First we compute $S(t',t)$ as follows:

   $$S(t,t') = \mathbb{P}[C_t > m, A_{t+m} > k] = \mathbb{P}[C_t > m]\mathbb{P}[A_{t+m} > k | C_t > m] = \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k),$$

   where the last equality follows from Assumption 2. Both $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$ and $\overline{\mathbf{F}}_{\mathbf{A_{t+m}}}(k)$ are decreasing in t because A_{t+x} and C_{t+x} are stochastically decreasing in t, for any $x \geq 0$ by Lemmas 5 and 7.
2. $v^{\tau^*}(NF',l,t') - v^{\pi_0}(.,.,t')$: This term is non-negative and decreasing in t using the induction assumption.

■

Proof of Theorem 3. We prove the optimality of $\tau^*(NF)$ formed in Proposition 2 by induction on n. Note that Proposition 2 required Assumptions 2-6 and 8. The proof additionally requires Assumption 7 to use Corollary 1 and Assumption 1 regarding decision points in the model.

- $n = 1$: The policy is optimal for $n = 1$ by construction.
- Assume the optimality of $\tau^*(NF)$ for $n = 1, \ldots, l$. We prove it for $n = l+1$.
  Fix NF, arbitrarily. We prove the optimality of τ^* based on whether $t \geq \tau^*(NF)$ or not as follows.

  $\rightarrow t \geq \tau^*(NF)$: The policy suggests no more surgeries. We argue its optimality as follows. We argue that the last l AVF chances will not be used. Note that these AVFs' possible use time will be at some $t' \geq t$ and for some $NF' \geq NF$. Since τ^* is optimal for $n \leq l$, $\tau^*(NF') \geq \tau^*(NF)$ (by Corollary 1), and that $t' \geq t \geq \tau^*(NF) \geq \tau^*(NF')$, these AVF chances will not be used . Thus, we are left with one AVF chance. Similarly, we should not use that chance, either. Thus, the no surgery decision is optimal in this case.

  $\rightarrow t < \tau^*(NF)$: The policy suggests surgery at t. We argue that it is optimal as follows. Assume the surgery is planned at $t' := t+y$. Note that no surgeries should be performed later than $\tau^*(NF)$ (using the logic explained in the first case). Thus, we restrict our attention to $t' < \tau^*(NF)$. For all such t', we have that $v(NF,n,t',0) = v^{\tau^*}(NF,n,t')$, based on the induction assumption. By this equality and Lemma 8, we have

  $$v(NF,n,t,y) = \overline{\mathbf{F}}_{\mathbf{C_t}}(y)\Big[v^{\tau^*}(NF,n,t+y) - v^{\pi_0}(.,.,t+y)\Big] + v^{\pi_0}(.,.,t)$$

  We conclude the proof by showing $v(NF,n,t,y)$ is decreasing in y. Since $\overline{\mathbf{F}}_{\mathbf{C_t}}(y)$ is decreasing in y and non-negative, it suffices to have that $v^{\tau^*}(NF,n,t+y) - v^{\pi_0}(.,.,t+y)$ is non-negative and decreasing in y which holds by Proposition 3, respectively.

■

Proof of Proposition 1. Fix NF, arbitrarily. Based on the way the optimal policy is formed in Proposition 2, we have that for all $t \in (0, \tau^*(NF))$, $v(NF,1,t,0) > v^{\pi_0}(.,.,t)$ and for all $t \in [\tau^*(NF), t_{\max}]$, we have $v(NF,1,t,0) \leq v^{\pi_0}(.,.,t)$. Since $v(NF,1,t,0) - v^{\pi_0}(.,.,t)$ is a decreasing continuous function, we can find $\tau^*(NF)$ using a binary search over $[0, t_{\max}]$. ■

Proof of Corollary 2. By Equation 9 and Lemma 10, we have that $d^{cr}(NF,t)$ is decreasing in t. The result then directly follows Equation 10. ■

Proofs of Theorems 6, 7:

Proof of Theorem 6. Fix $\Psi = \psi$ arbitrarily. The result generalizes using Lemma 2. Let $LT(y)$ and $L(y)$ be a patient's residual lifetime at t when the AVF surgery is planned at y with and without a potential transplant at $t = \psi$, respectively. We prove that $\overline{\mathbf{F}}_{\mathbf{LT(y)}}(a)$ is decreasing in y for any a. Let $Tr(\psi)$ be the patient's residual lifetime on transplant at ψ. We have:

$$\overline{\mathbf{F}}_{\mathbf{LT(y)}}(a) = \begin{cases} \overline{\mathbf{F}}_{\mathbf{L(y)}}(a) & : a \leq \psi \quad (15a) \\ \overline{\mathbf{F}}_{\mathbf{L(y)}}(\psi)\overline{\mathbf{F}}_{\mathbf{Tr}(\psi)}(a-\psi) & : \text{o.w.} \quad (15b) \end{cases}$$

Equation 15a follows from the fact that transplant benefits a patient's survival after the transplant, and Equation 15b follows our assumption that the lifetime of a patient on transplant does not depend on HD history. The result then follows by Theorem 1, which indicates that $\overline{\mathbf{F}}_{\mathbf{L(y)}}(x)$ is decreasing in y. ■

We use Lemma 11 to prove Theorem 7.

Lemma 11. *Consider the random variable Y, a function of the continuous random variable X, defined for $X = x$ as follows:*

$$Y(x) = \begin{cases} g(x) & : x \leq \theta; \\ g(\theta) + U & : x > \theta. \end{cases}$$

where g is a linear function. Then, we have $\mathbb{E}Y(X) = \mathbb{E}g(X) + \overline{\mathbf{F}}_{\mathbf{X}}(\theta)[U - \mathbb{E}g(X_\theta)]$

Proof. We have

$$\mathbb{E}[Y(X) - g(X)] = \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[Y(X) - g(X)\big|X > \theta] = \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[U + g(\theta) - g(\theta + X_\theta)], \quad (16)$$

$$= \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[U + g(\theta) - g(\theta) - g(X_\theta)] = \overline{\mathbf{F}}_{\mathbf{X}}(\theta)\mathbb{E}[U - g(X_\theta)], \quad (17)$$

where the first equality in Equation 16 follows the total law of probability and the fact that $Y = g$ for $X \leq \theta$, the second equality follows using the definition of Y and the identity $X|X > \theta = X_\theta + \theta$, and finally the first equality in Equation 17 follows by the linearity of g. ■

Proof of Theorem 7. In order to prove the theorem, we only show that Lemma 10 holds under the extended model as well. The rest of the proof follows similar steps taken for Proposition 2 and Theorem 3, which require Assumptions 1-8.

Let $\nu(NF, 1, t, 0)$ and $\nu^{\pi_0}(.,.,t)$ be the equivalents of $v(NF, 1, t, 0)$ and $v^{\pi_0}(.,.,t)$, respectively, under the model with the transplant option. Since monotonicity preserves under expectation, it suffices to prove the result under all possible scenarios (i.e., we use a sample path argument). Under the scenario where the transplant is canceled, we have $v(.) = \nu(.)$ and thus the result follows using Lemma 10. Now we consider the case of no cancellation. If the AVF does not mature, we have $\nu(NF, 1, t, 0) - \nu^{\pi_0}(.,.,t) = -d$, as the only difference in QALE is the AVF creation disutility. It remains to prove the result for the case of a successful AVF creation.

Fix $M = m$ arbitrarily. Let $t' := t + m$ be the time of switching to the matured AVF, and U be the lump-sum QALE the patient receives from transplant. Using Lemma 11 and by considering $g(x) = q_A x$, $X = A_{t'}$, and $\theta = \psi - t'$, we can show that the QALE residual at t' for a patient who is on an AVF from t' until transplant equals $q_A\mathbb{E}A_{t'} + \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')(U - q_A\mathbb{E}A_\psi)$. Similarly, we can show that the QALE residual at t' for a patient on the CVC equals $q_C\mathbb{E}C_{t'} + \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')(U - q_C\mathbb{E}C_\psi)$.

We can calculate $\nu(NF, 1, t, 0) - \nu^{\pi_0}(.,.,t)$ as follows:

$$\nu(NF, 1, t, 0) - \nu^{\pi_0}(.,.,t) = \overline{\mathbf{F}}_{\mathbf{C_t}}(m)\Big[\Big\{q_A\mathbb{E}A_{t'} + \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')(U - q_A\mathbb{E}A_\psi)\Big\} - \Big\{q_C\mathbb{E}C_{t'} + \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')(U - q_C\mathbb{E}C_\psi)\Big\}\Big] - d \quad (18)$$

Equation 18 can be explained as follows. The patient experiences a QALE difference starting from t' (AVF maturation time), but only if she survives until then. Therefore the QALE difference after t' is discounted by $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$. Since $\overline{\mathbf{F}}_{\mathbf{C_t}}(m)$ is decreasing in t (see the proof of Lemma 9), it suffices to prove that the term in the brackets, henceforth denoted by Δ, is non-negative and decreasing in t (or equivalently t'). By rearranging terms, we obtain :

$$\Delta = \Big[q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}\Big] + \Big[\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')q_C\mathbb{E}C_\psi - \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')q_A\mathbb{E}A_\psi\Big] + U\Big[\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') - \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big].$$

We have:

$$\begin{aligned}\Delta &\geq \Big[q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}\Big] + \Big[\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')q_C\mathbb{E}C_\psi - \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')q_A\mathbb{E}A_\psi\Big] \\ &\geq \Big[q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}\Big] + \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')\Big[q_C\mathbb{E}C_\psi - q_A\mathbb{E}A_\psi\Big] \geq 0.\end{aligned}$$

where the first inequality follows since $U \geq 0$ and $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') \geq \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$ as a consequence of Lemma 7, and the second inequality follows because again $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') \geq \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$. We have $q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'} \geq \overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t')\Big[q_A\mathbb{E}A_\psi - q_C\mathbb{E}C_\psi\Big]$ and thus the last inequality, because based on Theorem 2, $q_A\mathbb{E}A_t - q_C\mathbb{E}C_t$ is decreasing in t, $t' \leq \psi$, and $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') \leq 1$.

Finally, by rearranging terms in Δ, we can show that it equals the sum of the following decreasing functions:

- $q_A\mathbb{E}A_{t'} - q_C\mathbb{E}C_{t'}$: This term is decreasing based on Theorem 2.
- $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big[q_A\mathbb{E}A_\psi - q_C\mathbb{E}C_\psi\Big]$: Since $\overline{\mathbf{F}}_{\mathbf{C}}(t')$ is decreasing and $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t') = -\frac{\overline{\mathbf{F}}_{\mathbf{C}}(\psi)}{\overline{\mathbf{F}}_{\mathbf{C}}(t')}$ by definition, we have that $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$ is decreasing. Since $C_\psi \leq_{st} A_\psi$ based on Lemma 7, then using Assumption 8 we can show that $q_A\mathbb{E}A_\psi \geq q_C\mathbb{E}C_\psi$. Therefore, the term $-\overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big[q_A\mathbb{E}A_\psi - q_C\mathbb{E}C_\psi\Big]$ is decreasing.
- $\Big[\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') - \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')\Big](U - q_A\mathbb{E}A_\psi)$: This term is decreasing because $\overline{\mathbf{F}}_{\mathbf{A_{t'}}}(\psi - t') - \overline{\mathbf{F}}_{\mathbf{C_{t'}}}(\psi - t')$ is decreasing based on the theorem assumption, and $U \geq q_A\mathbb{E}A_\psi$ since we assume that a patient's residual QALE on transplant is higher than on HD.

■

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